FDG-PET/CT in staging and treatment of esophageal cancer

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Table of contents

Table of contents

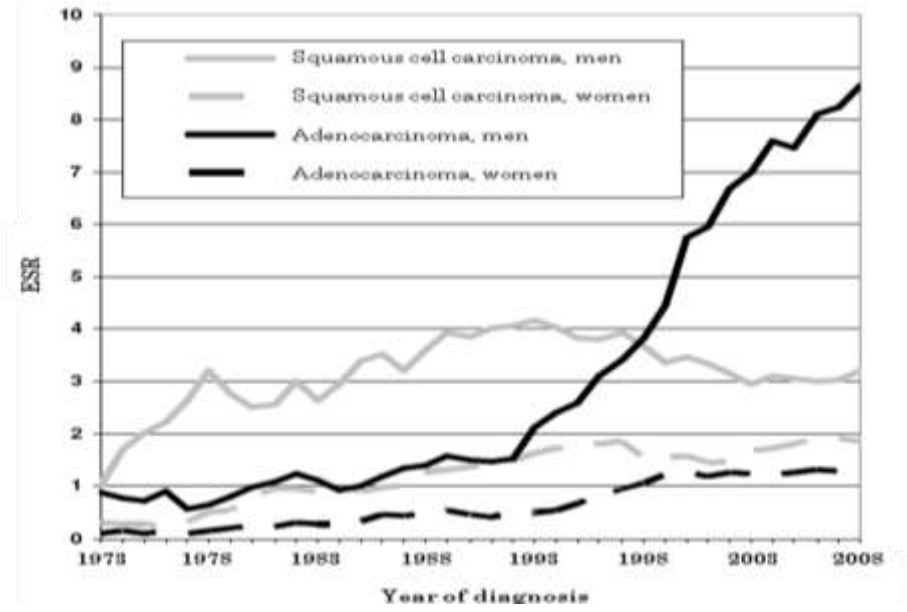
Part I

General Introduction

Epidemiology

As in many countries, the incidence of esophageal cancer in the Netherlands has increased steadily since the last decades. In 2009, 1900 new cases of esophageal cancer were diagnosed, which was only 684 new cases yearly two decades ago. This is mainly due to the fast rising number of esophageal adenocarcinoma in male (Figure 1). In the Unites States, as well as in many Western countries, the incidence of esophageal adenocarcinoma has increased a six-fold times surpassing squamous cell carcinomas as the most prevalent type of esophageal cancer.[1,2] Generally, esophageal cancer still has a high mortality rate with an overall five-year survival rate of 15% to 20% during the last decade.[3] The five-year survival rate in patients with a commonly presented adenocarcinoma of the distal esophagus after curatively intended surgery is 37%-51%, depending on the use of neoadjuvant treatment and the performed surgical technique.[4]

Figure 1. Age standardized number of new patients with esophageal cancer (1978-2008)



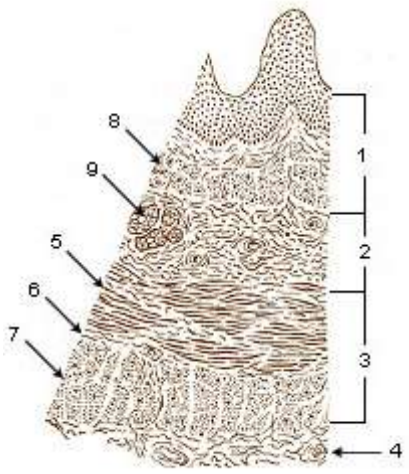
ESR: European Standardized Rate

Anatomy

The intrathoracic esophagus is divided into different subsides; (1) the upper thoracic part extending from the thoracic inlet to the level of the tracheal bifurcation, (2) the mid-thoracic part which is the proximal half of the esophagus between the tracheal bifurcation and the lower esophagus and (3) the lower thoracic part, which is the distal half of the esophagus between the tracheal bifurcation and the esophagogastric junction.

The wall of the esophagus is made up of four layers. From the inside out, (1) it starts with nonkeratinized stratified squamous epithelium, lamina propria and muscularis mucosae, which form together the mucosa. (2) The next layer is the submucosa which contains the mucous secreting glands (esophageal glands), blood vessels, lymphatic vessels, nerves and connective structures termed papillae. (3) The muscularis propria or muscularis externa follows, which consists of striated and smooth muscle. (4) The outer layer is called the adventitia (Figure 2).

Figure 2. The esophageal wall



1. Mucosa
2. Submucosa
3. Muscularis propria
4. Adventitia
5. Instraited muscle
6. Striated and smooth muscle
7. Smooth muscle
8. Lamina muscularis mucosae
9. Esophageal glands

Source:
http://training.seer.cancer.gov/ss_module07_ugi/unit02_sec04_anatomy.html

Staging

After the initial diagnosis, each patient has to be selected for proper individual treatment. Based on comorbidity information and current patient's condition we should assess whether patients are able to undergo a major surgical procedure (operability) and whether the tumor can be treated by curative intent. In other words, which patients are eligible for surgery and who is not? Proper patient selection is crucial and is only possible on the basis of adequate staging. Pretreatment clinical staging of esophageal cancer involves endoscopic ultrasonography (EUS), 64 multidetector/sliced computer tomography (md-CT), external ultrasound of cervical lymph nodes with the addition of positron emission tomography with 18-F-fluordeoxyglucose (FDG-PET) in the last decade. FDG-PET and more recently the hybrid PET-CT has made a rapid advance as "the staging modality" in the esophageal cancer workup. The optimal sequence of the different staging techniques, including EUS-FNA, md-CT, and FDG-PET remains unclear. Besides, the clinical relevance of ultrasound of the cervical area in detecting distant metastases remains a matter of debate.

Tumor-node-metastasis system

Esophageal tumors are classified according the tumor-node-metastasis (TMN) system of the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC).[5,6] The T categories assess primary tumor infiltration through the different layers of the esophageal wall into the surrounding structures and the N categories assess regional lymph node involvement. Distant metastases are classified in the M categories, such as haematogenous spread metastases in liver, bone, lung and brain tissue.

Between the sixth and the seventh edition (TNM-7), the classification of esophageal carcinoma's has undergone some major modifications in order to result in better prognostic stratification of overall survival. The categorization of

Table 1. Pathologic TNM classification of esophageal cancer according to the seventh edition of the UICC-AJCC

TNM stage	Description
T-stage	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High grade dysplasia
T1	Tumor invades lamina propria, muscularis mucosae, or submucosa
T1a	Tumor invades lamina propria, or muscularis mucosae
T1b	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades adventitia
T4	Tumor invades adjacent structures
T4a	Resectable tumor invading pleura, pericardium, or diaphragm
T4b	Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.
N-stage	
Nx	Regional nodes cannot be asessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases involving 1 to 2 nodes
N2	Regional lymph node metastases involving 3 to 6 nodes
N3	Regional lymph node metastases involving 7 or more nodes
M-stage	
M0	No distant metastases
M1	Distant metastases

T1 and T4 tumors has been extended to provide greater detail and the N categories are revised from side dependent staging to a classification which is based on the number of involved lymph nodes. Also new is the subdivision of celiac nodes within the definition of regional lymph nodes and the simplification of distant metastasis (M) into M0 and M1 rather than dependent on location (Table 1). One more improvement is the use of stage grouping and prognostic grouping. Stage grouping is based on anatomical stages and is applicable to all

types of carcinomas. Prognostic grouping separates adenocarcinoma from squamous cell carcinoma and ads histological stages to the T, N, and M categories.[7]

Preoperative diagnostics

Endoscopic ultrasonography

EUS is superior to other staging modalities in distinguishing tumor penetration into the different layers of the esophageal wall. It is therefore the investigation of choice with a sensitivity of 96%.[8-10] The accuracy of EUS can be improved by fine needle aspiration biopsies (FNAB) of suspicious lymph nodes and detectable lesions in the left liver and adrenal glands.[11-13] For that reason, EUS is more accurate in determine resectability than the latest 64-slided spiral CT scans with 5 mm slices.[14-17]

On the other hand, EUS has its own limitations; it reaches just as far as sound waves can penetrate into the tissues which is about 5-6 cm. For this reason it is impossible to examine distant metastasis in lymph nodes or organs. In 20-35% of all cases, stenotic esophageal carcinoma cannot be surpassed by the standard endoscope, which means that the staging remains incomplete. [18,19] In those cases when it is only possible to visualize the proximal part of the tumor, the accuracy of staging decreases to less than 50%. These difficulties can be overcome in different ways. A thin pediatric endo ultrasound scope (diameter 7.9 mm) can be used in an attempt to complete EUS staging. The accuracy of this scope may be equal to the standard scope, though it is only available in just a few Dutch centra. Alternatively, but still undesirable because of far-reaching complications, the stenosis can be dilatated step by step until a diameter of 16 mm has been reached, followed by EUS with a standard scope. In this way, up to 85% can be staged adequately with a standard endo ultrasound scope.[20] However, its main limitation is the possibility of esophageal rupturen at the tumor site with an higher risk of a decreased survival.

Computed tomography

CT scanning has an important contribution in the detection of distant metastases, especially in lungs, liver and adrenal glands. Furthermore, it is

possible to judge the locoregional growth of both primarily tumor and lymph node metastases on CT, though recent analyses show a low sensitivity (35-55%) and moderate specificity (71-100%) for the detection of locoregional lymph node metastases.[21,22] Judgment of tumor invasion into the aorta is based on the presence of a thin layer of fat over more than 90 degrees of the circumferential at the site of contact between tumor and aorta and on the infiltration of the triangle of fat between esophagus, aorta and the thoracic spine. For lymph node dissemination size criteria of a short-axis diameter larger than 10mm are used in case of mediastinal lymph nodes and a short-axis diameter of 8mm or more is used for lymph nodes at the hepatogastric ligament. What makes it difficult is the possibility of benign enlarged lymph nodes, for example in sarcoidosis and also in large, partly necrotic tumors, and the presence of micrometastases. Other criteria which rise the grade of suspicion are enhancement of the nodal capsule and poorly defined margins around the node.[24]

Positron emission tomography

In staging esophageal cancer with PET, a radio labeled glucose analog (18-F-fluoro-deoxy-D-glucose) is increasingly used which has a strong affinity for cancer cells. It visualizes glucose utilization and metabolic activity. In general, esophageal carcinoma show a good FDG uptake. In 82-100% the primary tumor is visualized, though with a sensitivity of barely 38%, it plays no significant role in T staging.[21] Besides of that, it is inferior to EUS in detecting locoregional lymph node metastases as well. Recent analyses show low sensitivity rates for both FDG-PET and CT (35-55%) and moderate specificity rates (71-100%) for this indication.[21,22] In other words; FDG-PET and CT are good at ruling locoregional lymph node involvement in, but not good at ruling it out. Only in determine distant lymph node dissemination, FDG-PET appears better than CT with a sensitivity of 58%-76% and a specificity of 90%-100%, compared to CT imaging with a sensitivity of 71% and a specificity of 93%. The relative

diagnostic odds ratio of FDG-PET vs.CT is 2.26 (95% CI 1.09-4.71, p<0.03), which illustrates a greater diagnostic value of FDG-PET regarding M staging.[25, 26] Recent studies show that the combination of FDG-PET and EUS-FNA results in improved pre-operative staging of esophageal and cardial cancer, and fusion of both diagnostics will alter the assessment of the tumor stage in 15-22%.[27-32]
Even with all of the abovementioned examinations, still 20 percent of all esophagectomies deal with distant metastases (M1) and/or infiltration in adjacent vital structures (T4). With optimizing the pre-operative staging, we hope for the highest quality of imaging in order to prevent unnecessary preoperative treatment and surgical explorations.

PET/CT

CT and FDG-PET are complementary techniques, in which CT-obtained information about anatomic structures will lead to an increased sensibility of physiologic PET-images based on an increased uptake of 18-Fluordeoxyglucose. Not much is known yet about hybrid PET/CT scanning in esophageal cancer, though it is likely that integrated PET/CT technology will gain influence in the next years. In staging lung cancer, accuracy improves considerably by direct coregistration of FDG-PET and CT, especially their specificity. It is very plausible that, to a greater or lesser extent, this is also true in case of esophageal cancers. Furthermore, known studies are based on first generation hybrid scanners.[33-38] Today's PET/CT scanners have both better camera sensitivity and higher resolution, which stands to reason that the accuracy of these scanners is higher, to a greater or lesser degree.

Therapeutic options

Surgery

For esophageal carcinoma staged as cT1-3N0-1M0, the treatment of choice still is a radical esophagectomy (with or without neoadjuvant chemoradiation), except for upper esophageal tumors which are treated with definitive chemoradiation therapy. Proximal carcinoma are treated with a thoracotomy or videoasisted thoracoscopy in order to remove the lymph nodes along the esophagus, trachea and the nodes located at the aortopulmonal window and infracardinal, together with a laparotomy in order to mobilize the stomach and to finish the lymph node dissection. In (adeno) caracinoma of the distal esophagus and gastroesophageal junction, a transhiatal esophageal resection without thoracotomy can be a good alternative. A third approach is a left sided thoracophrenicolaparotomy in case of tumors distally of the carina. The lymph nodes along the small curvation of the stomach, the left gastric artery and the celiac artery are resected *en bloc* with the tumor.[39] After surgery, the five-year survival rates intervene between 20 and 30%. They depend on surgical experience and hospital volume, and adequate preoperative staging.[40]

Postoperative mortality and morbidity rates depend on the extent of surgery. The pros and cons in deciding to operate and the choice of resection have to be carefully weight against other therapeutic options. Potentially curative resections are only possible in the absence of distant metastases and infiltration of the primary tumor into adjacent vital structures.

Preoperative chemo/radiation therapy

A variety of neoadjuvant regimens have been applied in order to improve locoregional control and survival. The role of neoadjuvant chemotherapy remains open since many years. In the updated Cochrane review published in 2010 there was no survival benefit for the group which received chemotherapy. The number of radical resections (R0) was not different between preoperative chemotherapy and surgery alone and there was no difference in mortality, non

fatal complications, and recurrences between both groups.[40] Yet in a meta-analysis of nine randomized controlled trials (eight of them were included in the Cochrane review), there was an absolute survival benefit in of 4.3% in five years and an absolute disease free survival benefit of 4.4% after five years.[41]

On the contrary, survival of patients with potentially curable esophageal carcinoma improves significantly if preoperative treated with a concurrent combination of Cisplatinum based chemotherapy and radiotherapy. It leads to better five-year survival rates (OR 1.46; 95%CI 1.07-1.99), a higher number of R0 resections, and equal postoperative complications. Unfortunately, it is attended with higher postoperative mortality rates (OR 1.68, 95%CI 1.03-2.73). Squamous cell carcinoma do not benefit from neoadjuvant chemoradiation.[42] Recently, a regimen of preoperative Carboplatin and Paclitaxel together with radiotherapy improved significantly the survival of patients with resectable esophageal cancer (CROSS-study). Complete resection with no tumor within 1 mm of the resection margins was achieved in 92% of patients after chemoradiation-surgery versus 69% in the surgery group with a median overall survival of 49.4 months versus 24.0 months, respectively. Complications rates and in-hospital mortality were similar in both groups.[43]

Unresectable disease

Some patients are beyond the scope of surgical therapy; patients not suitable for surgery because of their co-morbidities, patients with unresectable T4 tumors, patients with local recurrent disease, and patients with dissimilated disease. Some of these patients with localized disease may be considered for definitive radiotherapy, with or without chemotherapy. Concomitant chemoradiotherapy in patients who are not eligible for surgery because of severe comorbidity, leads to significantly better local control and survival than with radiotherapy alone, though a combined regimen has significantly more side effects than radiotherapy alone.[44,45]

In the palliative setting, stenting with self-expanding metallic stents (SEMS), external beam radiotherapy and/or brachytherapy are less invasive alternatives. Furthermore laser therapy and photodynamic therapy are good palliative options to reduce complaints such as dysphagia and pain and to improve prognosis.[46] Palliative resections will not increase survival rate nor enhance the quality of life and are therefore not recommended.

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Part II

Optimal Staging

Chapter 1

Current relevance of cervical ultrasonography in staging cancer of the esophagus and gastroesophageal junction

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Abstract

Purpose

To evaluate the value of external ultrasonography (US) of the neck in current dedicated preoperative staging of patients with cancer of the esophagus and gastro-esophageal junction (GEJ).

Materials and Methods

Diagnostic value of external US was analyzed in 180 consecutive subjects (154 men, 26 women, mean age 63 (38-84) years) without palpable cervical lymphadenopathy, treated between January 2001 and March 2006. Suspicious lesions were confirmed by cytological examination. In group A, all subjects (n=125) were staged by standard endoscopic ultrasonography (EUS), multidetector computed tomography (md-CT), positron emission tomography with 18F-fluorodeoxyglucose (FDG-PET) and external US. In a prospective group B of 55 subjects we used a revised protocol consisting of routine EUS and CT. PET was only indicated in subjects with T3-T4/N1 disease and external US was solely performed on indication.

Results

Cervical metastases were found in seven subjects from group A (6%) and in five from group B (9%). Eleven of these metastases were detected by US and nine on CT. All nodal metastases were detected by the combination of PET and CT. Twenty percent (4/20) of the tumors above the carina and 5% (8/160) of the distal tumors presented with cervical metastases. All were diagnosed as T3 and T4 tumors on EUS. No cervical metastases were missed by the diagnostic algorithm in group B.

Conclusion

In present staging procedures for esophageal cancer, routine external US has no additional value in detecting cervical metastases. It is only indicated to obtain cytological proof of suspected cervical lesions.

Introduction

According to their anatomic location, lymph node metastases are strongly correlated with stage and prognosis in esophageal cancer. Nodal metastases in esophageal cancer are frequently found in the neck (22%), upper (34%), mid (23%) and lower mediastinum (20%), and in the upper abdomen (38%).[1] Tumors with upward lymphatic spread usually metastasize to the cervical nodes, nodes along the recurrent nerves and infra-aortic nodes and those with downward lymphatic spread metastasize to the subcarinal and para-esophageal nodes and nodes along the left gastric artery.

Radical esophagectomy en-bloc with regional lymphadenectomy is still the treatment of choice in patients with cancer of the esophagus and GEJ.[2] Since the introduction of neoadjuvant treatment in gastroesophageal tumors, the results have improved markedly.[3] In particular, the use of preoperative chemoradiation led to a considerable downstaging effect on these tumors with a subsequent better survival.[2,4,5] However, curative resections are only possible in the absence of distant metastases (M1b) and invasion of the primary tumor into adjacent vital structures (T4). Palliative resections will not increase the survival rate nor enhance the quality of life.[6]

Adequate preoperative staging is crucial for appropriate patient selection preventing unnecessary preoperative treatment and surgical explorations and for accurate comparison of treatment results between institutes. Nevertheless, approximately 20% of all esophageal cancer resections don't achieve their curative intent. Staging usually includes endoscopic ultrasonography (EUS) eventually with fine needle aspiration (FNA), thoracic and abdominal computed tomography (CT), and external ultrasonography (US) of the neck region. EUS is the most accurate method to assess local invasion of the primary tumor and locoregional lymph node involvement with an overall accuracy of 85-90% and 70-80%, respectively.[7] CT and external US are both non-invasive modalities for identifying distant metastatic disease.[8, 9] The sensitivity and specificity for cervical node metastasis are 37% and 97% for CT and

57-71% and 97-100% for external US.[10] Positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET) is a relatively new non-invasive staging method for improving the accuracy of detecting both lymphatic (sensitivity: 82%, specificity 60%) and distant metastases (sensitivity: 81%, specificity: 91%).[11-16] With the enhanced quality of current multidetector CT (md-CT) scans and the application of PET, the value of external cervical US in a standard staging protocol is questionable.

The aim of this study was to assess the role of cervical US in the current staging work-up for esophageal cancer patients.

Materials and Methods

General methods

The value of cervical US in detection of cervical metastases was analyzed in 180 consecutive subjects staged during the period January 2001 through March 2006. In group A (n=135) a standard preoperative work-up was performed, consisting of cervical, thoracic and abdominal md-CT, EUS, FDG-PET and external US of the neck. The detection of cervical metastases was solely based on CT/PET and US.

In a previous study all FDG-PET positive foci were found in ≥T3 or N+ stages.[17] Based on these results and the outcomes of group A, 55 subjects (group B) were staged according to a new diagnostic algorithm.(Table 1). In this prospective study, all subjects underwent a preoperative work-up consisting of EUS-FNA and md-CT of the neck, thorax and abdomen, and additionally by PET in subjects with advanced disease, defined as T3/T4 and/or N1 disease. External US of the neck was only performed on indication, such as suspected or aberrant lesions seen on CT and/or hotspots on PET scan at the cervical region. In both studies an informed consent was given by all subjects.

Subjects were staged according to the latest tumor-node-metastasis (TMN) system of the Union Internationale Contre le Cancer (UICC). Depending on tumor invasion and lymph node involvement they were divided into stage I (T1N0M0), stage II (T2-3N0M0/T1-2N1M0), stage III (T3N1M0/T4N0-1M0) or stage IV (T1-4N0-1M1). Cervical node metastases were considered to be distant metastases (M1b) in mid and distal esophageal tumors. Suspect cervical lesions were confirmed by fine needle aspiration cytological examination (FNAC). Pathological outcome and/or clinical evidence of progressive disease during the first 12 month of follow-up were used as gold standard.

Table 1.Clinical and pathologic factors in both groups

Characteristics	Group A n=125 (%)	Group B n=55 (%)
Gender		
Male	103 (82.4)	51 (92.7)
Female	22 (17.6)	4 (7.3)
Age (years)		
Mean (range)	63.1 (38-81)	64.0 (44-84)
Histology		
AC	103 (82.4)	41 (74.5)
SC	22 (17.6)	10 (18.2)
Other	0 (0.0)	3 (5.5)
Unknown	0 (0.0)	1 (2.0)
Localization		
High	16 (12.8)	4 (7.3)
Low	78 (62.4)	39 (70.9)
GEJ	31 (24.8)	12 (21.8)
Clinical staging		
Stage I	8 (6.4)	2 (3.6)
Stage II	32 (25.6)	14 (25.4)
Stage III	59 (47.2)	16 (29.1)
Stage IV	26 (20.8)	23 (41.8)

AC: adenocarcinoma, SC: squamous cell carcinoma.

Subjects

In group A, the medical records of 135 patients with cancer of the thoracic esophagus or GEJ, diagnosed between January 2001 and June 2005, were retrospectively reviewed. Ten subjects were excluded from further analysis because ultrasonography of the neck was not performed. For 120 out of the 125 included subjects all staging methods were performed and were available for statistical analysis. In the remaining subjects CT data were missing for various reasons; in two subjects CT imaging was not possible because of co-morbidity (n= 1) and refusal by subject (n= 1) and missing CT data (n=3) acquired in local hospitals.

Since June 2005, 55 consecutive subjects were prospectively staged according to the new diagnostic algorithm (group B) based on earlier research.[18] Forty-four subjects with T3/T4 and/or N1 were additionally staged with PET (Table 2). External US was performed ten times on the basis of deviant CT findings (n=4), suspicious hotspots on PET (n=2) or both (n=4). FNA was performed eight times because of lymphadenopathy (n=7) and one thyroidal node (n=1) (Figure 1). One subject was excluded from the analyses as US was performed solely to achieve cytological proof of a solid node palpable lesion in the thyroid.

Endoscopic ultrasound

A radial scanner (GF-UM 130 or GF-UM 160, 5-20 MHz, Olympus Medical Systems, Tokyo, Japan) was used for EUS. FNA of suspected lymph node metastases was obtained via a separate linear-array echoendoscope (FF-UC140P, Olympus Medical Systems, Tokyo, Japan or FGUX-36, 5-7.5 MHz, Pentax, Benelux, Breda, The Netherlands) with a 22-Gauge needle (Echotip, Wilson-Cook Medical Inc., Winston-Salem, NC, USA). In stenotic tumors, not traversable by the standard echoendoscope, a small-caliber probe (MH-908, 7.5 MHz, Olympus Medical Systems, Tokyo, Japan) was used in an attempt to pass the tumor. EUS was achieved with the subject in a left decubitus position under sedation using 2.5-10 mg midazolam intravenously.

Computed tomography

Computed tomography was performed using a md-CT scanner (Somatom Sensation 16 Siemens, Medical Systems, Erlangen, Germany.) Md-CT scans were obtained with 3 mm and 5 mm collimation. Scans with both intravenous and oral contrast fluid were performed from the lower neck, chest, and the entire liver. Enhanced cervical lymph nodes were suspicious in case of enhancement of the nodal capsule and if the margins around the node were poorly defined. A minimum axial nodal

diameter larger than 11 mm for jugulodigastric nodes and 10 mm for all other cervical nodes, was suspected for malignancy.[19]

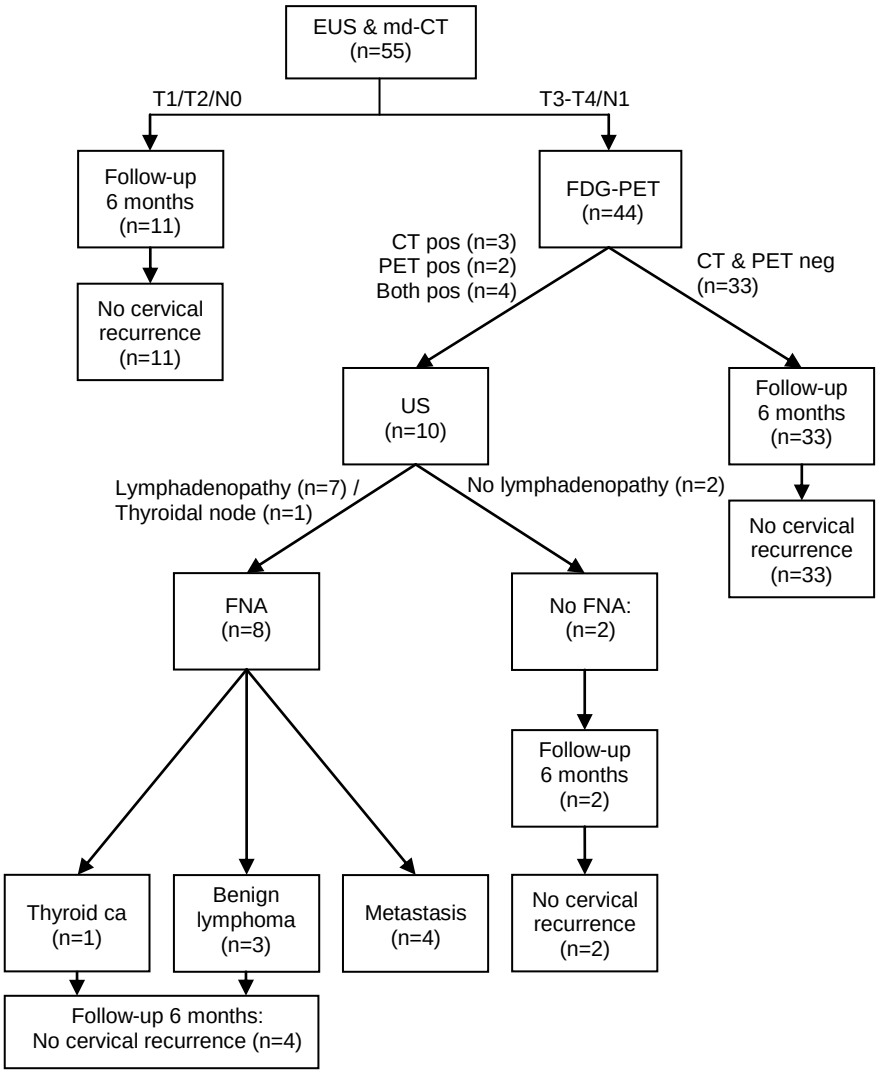
External ultrasonography of the neck

External US was performed by or under direct supervision of an experienced radiologist at the University Medical Center Groningen using a 7.5-13.5 MHz linear array transducer (Siemens Antaris, Siemens Medical Systems, Erlangen, Germany). Round hypo-echoic lymph nodes larger than 5 mm, clearly delineated with a scattered internal echo were suspected for malignancy and confirmed cytologically by ultrasound-guided FNA with a 22-Gauge needle.

Positron emission tomography with 18-fluorodeoxyglucose

FDG-PET was performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA). The 951/31 acquires 31 planes over 10.9 cm, the HR+, 63 planes over a 15.8 cm axial field of view. All subjects fasted for over 4 hours before a mean dose of 400 to 580 MBq FDG (depending on body weight) was administered intravenously. Data acquisition started in whole body mode 90 minutes after injection, for 5 minutes per bed position from the crown to the mid femur. All PET scans were originally interpreted by one or two experienced nuclear medicine physicians.

Figure 1. Flowchart of the diagnostic pathway in group B.



EUS: endoscopic ultrasonography, md: multidetector, CT: computed tomography, FDG: ^{18}F-fluorodeoxyglucose, PET: positron emission tomography, US: ultrasound, pos: positive, neg: negative, ca: carcinoma.

Table 2. Different staging modalities in both groups

Investigations	*Group A*	*Group B*
	n=125	*n=55*
Conventional staging		
EUS	125	55
Md-CT	120	55
US of the neck	125	11
FNA during US	37	8
Additional staging		
FDG-PET	125	44

EUS: endoscopic ultrasonography, md: multidetector, CT: computed tomography, US: ultrasound, FDG: ^{18}F-fluorodeoxyglucose, PET: positron emission tomography

Statistical analyzes

To estimate the value of different staging modalities, in particularly external ultrasonography, staging investigations were performed within a two week period and the diagnostic work-up was documented. Sensitivity, specificity and accuracy were calculated separately in both groups for US, md-CT, PET and for md-CT together with PET.

Results

Group A

Subject and tumor characteristics are summarized in Table 1. The mean age was 63 (38-81) years. One-hundred-and-three subjects (82%) had an adenocarcinoma, the majority of which were located in the distal esophagus; 78 (62%) were located between the carina and GEJ and 31 (24.8%) at the GEJ. Cervical metastases were present in seven out of the 125 subjects cervical metastases with a negative physical examination (Table 3). None of the subjects with T1-2N0 (n= 15 subjects) in this group had positive cervical node findings. Traditionally, CT is the initial staging test to detect distant metastases, but cervical metastases were only identified in five cases on CT of the neck (subjects 6, 7, 8, 9, 10). PET imaging detected suspect cervical foci in ten subjects. One of the hotspots was suspicious for a synchronous primary tumor in the thyroid. Histological exam revealed a Hürthlecell tumor (subject 3). In two subjects indeterminate suspect hotspots were seen. One of the hotspots appeared to be a benign lymphoma (subject 1) and the other a cystic, degenerative, dysplastic thyroid nodule (subject 2). All cervical node metastases were identified by the combination of PET and CT. Six out of seven subjects with cervical metastatic disease were identified by external US, but only five were confirmed by cytology. In subject 8 histological examination was not performed because of metastatic disease in the right kidney and trunk region. In subject 7 a deep paratracheal malignant lymph was missed during the routinely performed US and cytology (during a second US) was inconclusive. In the last two subjects a 12 month clinical/radiological follow-up was taken as validation.

Table 3. Subjects with suspect cervical findings in group A

	Suspect findings seen by:				
Pt.nr	**CT**	**PET**	**US**	**Cytology**	**Outcomes**
1	no	Ind	no	Benign	No metastasis
2	no	Ind	no	Benign	Thyroidal node
3	no	Yes	no	Benign	Follicular adenoma
4	no	Yes	yes	Malignant	Metastasis
5	no	Yes	yes	Malignant	Metastasis
6	yes	Yes	yes	Malignant	Metastasis
7	yes	Yes	no	Se	Progressive disease
8	yes	Yes	yes	-	Progressive disease
9	yes	Yes	yes	Malignant	Metastasis
10	yes	Yes	yes	Malignant	Metastasis
Total	**5**	**8**	**6**		**7**

Pt.nr: subject number, CT: computed tomography, PET: positron emission tomography, US: ultrasound. Ind: indeterminate, Se: sampling error (not enough cells, progressive disease: evidence of disease during first six month of follow-up

Group B

Fifty-five subjects were included in group B. The mean age was 64 (44-84) years. In 41 subjects an adenocarcinoma was present and in 51 subjects the primary tumor was localized beneath the carina. Locally advanced esophageal cancer was present in 29 % and in 42% metastatic disease was present (Table 1). In five subjects nodal malignancy was cytologically proven (n=4) or clinical follow up during the first 12 months (n=1) (Table 4). All these cases were detected whilst implementing the new diagnostic algorithm which combines the use of md-CT and PET; three were detected by PET and CT (subject 18, 19, 16), one by PET alone (subject 12) and in one subject PET information, acquired in a local hospital, was deficient for unknown reasons (subject 17). All metastases were also seen during cervical US and confirmed by cytological examination. In one subject, however (subject 16), sampling error must have occurred and diagnostic validation was by clinical/radiological follow-up. Besides these five subjects there were four other subjects with aberrant

findings on imaging evaluation (subject 11, 13, 15, 14). In subject 11 a node in the thyroid gland was seen during cervical US which was also seen on PET. FNA-cytology revealed a squamous cell carcinoma of the thyroid gland, while the esophageal cancer was of the adenocarcinoma type. In three other subjects indeterminate abnormalities were seen; two appeared to be benign lymphoma (subject 13, 14) and one was a follicular adenoma (subject 15).

Table 4. Subjects with suspect cervical findings in group B

	Suspect findings seen by:				
Pt.nr	**CT**	**PET**	**US**	**Cytology**	**Outcomes**
11	no	Yes	node in thyroid	Malignant	Squamous cell ca of the thyroid gland
12	no	Yes	yes	Malignant	Metastasis
13	ind	No	ind	-	No metastasis
14	ind	No	ind	Benign	No metastasis
15	ind	Ind	ind	Benign	Follicular adenoma
16	yes	Yes	yes	Benign (se)	Progressive disease
17	yes	-	yes	Malignant	Metastasis
18	yes	Yes	yes	malignant	Metastasis
19	yes	Yes	yes	Malignant	Metastasis
Total	**4**	**5**	**5**		**5**

Pt.nr: subject number, CT: computed tomography, PET: positron emission tomography,
US: ultrasound, Ind: indeterminate, se: sampling error, progressive disease: evidence of disease during first six month of follow-up

Tumor localization, type and stage versus cervical dissemination

Of the twelve subjects with cervical node metastases, four had a primary tumor located above the level of the carina (4/20; 20%) and eight had a distal tumor below the carina (8/160; 5%). Nine tumors (9/144; 6%) were adenocarcinoma's and three squamous cell carcinoma's (3/32; 9%). Eleven of these 12 tumors were staged as T3 (11/146; 8%) and one as T4 (1/7; 14%) on EUS.

Table 5. Comparison of outcomes for US, md-CT and PET

	*Gold standard**								
	(+)		(–)		Total				
	A	**B**	**A**	**B**	**A**	**B**		**A**	**B**
US of the neck (I)									
(+) outcomes	6	5	0	3	6	8	**Sensitivity**	86%	100%
(–) outcomes	1	0	118	3	119	3	**Specificity**	100%	50%
Total	**7**	**5**	**118**	**6**	**125**	**11**	**Accuracy**	**99%**	**73%**
md-CT(II)									
(+) outcomes	5	4	0	3	5	7	**Sensitivity**	71%	80%
(–) outcomes	2	1	113	47	115	48	**Specificity**	100%	94%
Total	**7**	**5**	**113**	**50**	**120**	**55**	**Accuracy**	**98%**	**93%**
FDG-PET (III)									
(+) outcomes	8	4	2	2	10	6	**Sensitivity**	100%	100%
(–) outcomes	0	0	115	38	115	38	**Specificity**	98%	95%
Total	**8**	**4**	**117**	**40**	**125**	**44**	**Accuracy**	**98%**	**95%**
CT + PET (IV)									
(+) outcomes	8	4	1	1	9	5	**Sensitivity**	100%	100%
(–) outcomes	0	0	111	39	111	39	**Specificity**	99%	98%
Total	**8**	**4**	**112**	**40**	**120**	**44**	**Accuracy**	**99%**	**98%**

US: ultrasound, md: multidetector, CT: computed tomography, FDG: ^{18}F-fluorodeoxyglucose, PET: positron emission tomography, (I) cervical US findings versus gold standard, (II) md-CT findings versus gold standard, (III) FDG-PET findings versus gold standard, and (IV) md-CT + FDG-PET findings versus gold standard, A: group A, B: group B. *Gold standard: histopathologic conclusions and/or clinical evidence of disease during the first six month of follow-up

Performance of diagnostic modalities

The diagnostic accuracy of US, md-CT and PET for both groups is summarized in table 5. Suspicious cervical lymph nodes were detected by US in 10% (14/136), three of which were false positive. Sensitivity of external US increased from 86% to 100%, and specificity decreased from 100% to 50% by applying US only on indication. The sensitivity, specificity and accuracy of PET together with md-CT in the assessment of cervical metastases were similar in both groups; 100%, 99% and 99% respectively in group A and 100%, 98% and 98% respectively in group B. Because PET is not yet

generally accepted as part of the standard diagnostic work-up, we also compared the accuracy of both standard and additional US with that of md-CT without PET (Table 5). The sensitivity of md-CT was 71% and 80%, specificity was 100% and 94%, and the accuracy was 98% and 93% in group A and B, respectively.

Discussion

The results of this study show that US of the neck is of limited value in detecting cervical node metastases in patients with cancer of the esophagus and GEJ following a protocol, consisting of EUS and md-CT and with PET in case of T3-T4 and/or N1 disease. External US did not improve the accuracy of staging nor change patient management. Hence, it should not be implemented in standard preoperative work-up, but should be performed only on indication, such as to achieve cytological proof. It is debatable whether external US should be a standard investigation in patients with a tumor above the level of the carina, as it is suspected that this subgroup predominantly disseminates upwards.[20, 21] They encompassed 33% (4/12) of all cervical metastases in our study population, despite high tumors accounting for only 11% (20/180).

Further analysis of different staging modalities revealed that md-CT on its own was not sensitive (sensitivity in both groups together: 75%) enough to detect cervical metastases. In three subjects (3/12), md-CT missed cervical dissemination located in areas III and IV. Artifacts seem to be the main reason for the difficulties in delineating metastases in areas III and IV clearly. By adding PET to the diagnostic work-up in T3-T4/N1 disease, all cervical node metastases were recognized. PET has an incremental value, especially in determining nodal involvement in the neck areas III and IV. On the other hand, specificity decreased (specificity md-CT: 98%, specificity md-CT plus PET: 95%) due to 31% (5/16) false positive findings seen on PET. False positive findings are usually caused by inflammatory or reactive tissue and are easily assessed by additional investigations like physical examination or ultrasonography with FNA. All non-metastatic causes of abnormal FDG accumulation in our study were clarified by these benign causes of FDG uptake or by synchronous malignancy in the thyroid gland. The false negative rates for all tests were low because of the small number of positive findings. PET is not generally available in many developed countries and in clinics without PET techniques, US will have an incremental value in detecting cervical nodal spread. In that case we

suggest performing US only in T3/T4 and/or N1 tumors, as in our study only these tumors metastasized to the neck.

We found a prevalence of 7% (12/180) of cervical lymph node metastasis in cancer of the thoracic esophagus and GEJ. US revealed positive findings in 8% (14/180) with a sensitivity of 92%, specificity of 98% and accuracy of 97%. The reported rate of cervical metastases varies between 4% and 31%. Tachibana et al. found 4% (11/266) malignant cervical lymph nodes in patients with thoracic esophageal cancer.[20] Doldi et al. found a prevalence of 10% (18/174), but they included neoplasms of the hypopharynx and cervical esophagus.[21] Natsugoe et al. reported a higher percentage of 31% (160/519), although they did not clarify whether patients with carcinomas of the cervical esophagus and hypopharynx were excluded.[22] Shiozaki, also reported a high percentage of cervical lymphadenopathy in thoracic esophageal cancer of 27% (25/91).[23] In these last two studies pathological proof was achieved by neck dissection, which might be the explanation for this high prevalence. .

In conclusion, this study shows that routine external US of the neck is not useful in detecting cervical node metastases in patients with cancer of the esophagus and GEJ after dedicated staging. However, we like to stress that external US is still indicated to achieve cytological proof of lymph nodes suspected for metastasis by guided biopsy.

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Chapter 2

Better Assessment of Nodal Metastases by PET/CT Fusion compared to side-by-side PET /CT in Oesophageal Cancer

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Abstract

Background

Recently, positron emission tomography/computed tomography (PET/CT) has been introduced in the staging of oesophageal cancer. The impact of PET/CT fusion in comparison to side-by-side PET/CT in these tumours, was analyzed.

Patients and Methods

In 61 patients, 18-F-fluorodeoxyglucose (FDG)-PET and multidetector (md)-CT were performed within a two week interval. Software-fusion of md-CT and FDG-PET was correlated with side-by-side FDG-PET/CT reading by two independent investigators. The gold standard was the pathological outcome or clinical evidence of progression during the first year of follow-up.

Results

In 18 patients (18/61; 30%), nodal staging improved with software-fusion. The number of nodal metastases increased in five patients and decreased in four patients, leading to up-staging in one patient (2%) and down-staging in three patients (5%). In nine cases (15%), certainty and localization of metastases improved. However, the number of distant metastases did not change and software-fusion did not have an influence on resectability.

Conclusion

PET/CT fusion substantially improves detection and localization of nodal metastases and may have an impact on locoregional treatment options.

Introduction

In cancer of the oesophagus and gastro-oesophageal junction (GOJ) curatively intended resection, eventually with neoadjuvant chemoradiation, is the most effective treatment option.[1] As cure is only possible in the absence of distant metastases or local invasion into vital surrounding structures, optimal staging is indispensable for adequate preoperative patient selection preventing unnecessary surgical exploration.

Endoscopic ultrasonography (EUS) in combination with fine needle aspiration (FNA), multidetector computed tomography (md-CT), and ultrasound (US) of the cervical region are commonly used staging methods.[2] EUS-FNA is the most accurate in detecting nodal involvement and gross mediastinal invasion, whereas CT is the best imaging technique in detecting distant metastases.[3] In the last decade, positron emission tomography with 18-F-fluorodeoxyglucose (FDG-PET) has become a frequently used staging technique.[4-7] FDG-PET is especially applied for the detection of regional lymph node and distant metastases not visible on CT or EUS. Hence, pre-therapeutic FDG-PET alters assessment of the tumour stage in 15-22% of the patients.[8-12]

Despite the improvements in preoperative staging, it is still difficult to determine resectability accurately. Depending on the pre-operative work-up, local invasion and distant metastases are found in 10-60% of patients during exploration.[13-20] A combination of PET/CT images is thought to increase significantly the accuracy of staging because it correlates functional PET information with high resolution anatomical CT results.[21-26] Previously, it was common practice to correlate FDG-PET with CT visually, but recently hybrid PET/CT or PET/CT fusion have gained more support. In this study the accuracy of PET/CT fusion in staging patients with cancer of the oesophagus or GOJ was evaluated and compared with visual correlation of PET and md-CT.

Patients and Methods

Patient characteristics

Retrospectively the medical records of 85 patients, who were staged by FDG-PET and md-CT and treated for cancer of the oesophagus or GOJ between January 2001 and November 2004 were analyzed. Exclusion criteria were, treatment with neoadjuvant chemoradiation or a history of other malignancies. Twenty-four patients were excluded, either because the CT data from rural hospitals were missing (n=10) or the CT-slices were too thick (n=14). All the other patients were staged with EUS, 16-64 md-CT with slices of at least three mm and FDG-PET within two weeks of the time of presentation. In these 61 patients, it was feasible to perform a software-based PET/CT fusion. The mean age was 63.4 (SD±8.0; range 48-80) years (Table 1). Fifty patients (82%) presented with an adenocarcinoma of the oesophagus. Most of the tumours (87%) were localized in the distal part of the oesophagus (n=40) or at the GOJ (n=13). Depending on tumour invasion and lymph node involvement, the tumours were divided into stage I-IV according to the tumour-node-metastasis (TMN) staging system of the Union Internationale Contre Le Cancer (UICC).[27]

Computed tomography

Multidetector row CT imaging was performed with a 16-64 md-CT scanner (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). The CT scans (collimation 16 x 1.5 mm) were performed from the neck to the upper abdomen with both intravenous and oral contrast. The reconstructed slices had a thickness of 3 mm with a 1.5 mm effective section thickness.

Table 1. Patient characteristics

Characteristics	N (%)
Gender	
Male	51 (83.6)
Female	10 (16.4)
Age (years)	
Median (Range)	63.4 (48-80)
Histology	
Adenocarcinoma	50 (82.0)
Squamous cell carcinoma	11 (18.0)
Localization	
High	8 (13.1)
Low	40 (65.6)
GOJ	13 (21.3)
Clinical staging	
Stage I (T1N0M0)	4 (6.6)
Stage II (T2-3N0M0/T1-2N1M0)	18 (29.5)
Stage III (T3N1M0/T4N0-1M0)	32 (52.5)
Stage IV (T1-4N0-1M1)	7 (13.7)
Total	**61**

Clinical stage: staging without software based FDG-PET/CT, GOJ: gastro-oesophageal junction

Positron emission tomography with 18-fluorodeoxyglucose

FDG-PET was performed with an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA) acquiring 63 planes over a 15.8 cm axial field-of-view with retractable septa that enable 2D or fully-3D data acquisition. All patients fasted for at least 4 hours before 400 - 580 MBq FDG (depending on body weight) was administered intravenously. The transmission scans were performed for 3 minutes per bed position allowing attenuation correction. The scans were corrected for decay, scatter and randoms, whilst the ordered subset expected maximization with two iterations and 16 subsets was used for reconstruction. A Gaussian filter of 5 mm full width at half maximum was used for post-

smoothing of the reconstructed images.[28] Data acquisition started in whole body mode 90 minutes after injection, for 5 minutes per bed position from the crown to the mid-femur.

Diagnostic evaluation of CT and PET findings

The images of the md-CT, EUS and FDG-PET techniques were reviewed independently by two experienced nuclear physicians. Round hypo-dense lymph nodes larger than 5 mm and lymph nodes measuring 10 mm or more on CT were determined to be pathological. Pathological lymph nodes at the celiac axis were classified as M1a metastases in the case of distal oesophageal cancer or as M1b metastases in the mid or proximal tumours. Cervical metastases were classified as M1a in the case of proximal cancer and as M1b for mid or distal tumours. The FDG-uptake was scored on a four-point intensity scale: 'normal' (physiological), 'slightly increased', 'moderately increased' and 'intensely increased'. These lesions were interpreted as: 'absolutely benign', 'probably benign', 'indeterminate', 'probably malignant' and 'definitely malignant'. All the 'indeterminate', 'probably malignant' and 'definitely malignant' lesions were identified as hotspots. Suspect lesions were occasionally confirmed by FNA cytology, by pathological examination during or after surgery, or by radiological and clinical follow-up of at least one year. The lymph nodes were defined according to the Naruke lymph node stations (Table 2).

PET/CT fusion compared with side-by-side PET/CT reading

Together with an experienced radiologist all the reviewed FDG-PET and CT results were visually correlated (side-by-side) and scored by the same nuclear medicine physicians. Lymph nodes >1 cm on CT imaging without FDG-uptake on PET imaging, were scored as negative on visually correlated FDG-PET/CT staging. The

Table 2. Locoregional and distant lymph node stations according to Naruke

Stat.	*Name*	Location
1	Supraclavicular	Above suprasternal notch and clavicles
2R	Right upper paratracheal	Between intersection of caudal margin of innominate artery with trachea and the apex of the lung
2L	Left upper paratracheal	Between top of aortic arch and apex of the lung
3P	Posterior mediastinal	Upper para-oesophageal nodes, above tracheal bifurcation
4R	Right lower paratracheal nodes	Between intersection of caudal margin of innominate artery with trachea and cephalic border of azygos vein
4L	Left lower paratracheal	Between top of aortic arch and carina
5	Aorto-pulmonary	Subaortic and para-aortic nodes lateral to the ligamentum arteriosum
6	Anterior mediastinal	Anterior to ascending aorta or innominate artery
7	Subcarinal	Caudal to the carina of the trachea
8	Para-oesophageal	From the tracheal bifurcation to the diaphragm
9	Pulmonary ligament	Within the inferior pulmonary ligament
10R	Right tracheobronchial	From cephalic border of azygos vein to origin of RUL bronchus
10L	Right tracheobronchial	Between carina and LUL branches
15	Diaphragmatic	Lying on the dome of the diaphragm, and adjacent to or behind its crura
16	Paracardial	Immediately adjacent to the gastro-oesophageal junction
17	Left gastric	Along the course of the left gastric artery
18	Common hepatic	Along the course of the common hepatic artery
19	Splenic	Along the course of the splenic artery
20	Celiac	At the base of the celiac artery

Stat.: station, L: left, R: right, RUL: right upper lobe, LUL: left upper lobe

rigid software-based PET/CT fusion was accomplished on a Siemens Leonardo Workstation using the Syngo 3D Fusion program. Fusion was carried out and PET/CT images were scored by the same experienced nuclear physician and

radiologist. Disagreement was resolved in a consensus meeting. The outcomes of software fusion were compared with visually correlated PET/CT and the differences between these two methods were scored as shown in Table 3.

Enlarged lymph nodes > 1 cm on CT with negative PET findings were defined as negative. In the cases where fusion detected nodes that were initially not seen at all on md-CT or seen but not classified as physiological lymph nodes, these PET positive nodes were retrospectively defined as positive lymph nodes.

The grade of certainty increased (outcome 2), when: the lymph nodes were detected retrospectively at the anatomic location of FDG-accumulation; the lymph nodes with a moderate suspect diameter or appearance turned out to be PET positive; the nodes at fusion were defined at another anatomical location than that seen by side-by-side review, but within the same TNM stage or when fusion revealed FDG accumulation in a suspicious node located in the proximity of the primary tumour which was unclear for PET positivity on side-by-side correlation .

Table 3. Improvements of software based FDG-PET/CT fusion compared with visual side-by-side correlation

	Outcomes	**N=61 (%)**
1	No improvement	43 (70)
2	Staging unaltered, increased certainty of suspicion or location	9 (15)
3	Staging unaltered, number of metastases increased	4 (7)
4	Staging unaltered, number of metastases decreased	1 (2)
5	Staging unaltered, localization altered	0 (0)
6	Upstaging, not leading to changes in resectability	1 (2)
7	Upstaging, change in resectability from resectable to irresectable	0 (0)
8	Downstaging, not leading to changes in resectability	3 (5)
9	Downstaging, change in respectability from irresectable to resectable	0 (0)

Follow-up

The follow-up data of all the patients were available. The patients were followed according to a standardized programme consisting of an examination at the

outpatient department every three months for the first two years and every six months thereafter for a total period of five years.

Statistical analysis

Sensitivity, specificity and accuracy were calculated for both visual correlation and PET/CT fusion. Both the techniques were compared in nonparametric paired analysis using the McNemar test and p-values < 0.05 were considered statistically significant.

Results

In 18 patients (30%), an improvement in the detection of locoregional and/or distant lymph node metastases was observed on fused PET/CT compared to visually correlated CT and PET (Table 3). Details of these 18 patients are summarized in Table 4.

Increased certainty of localization and number of metastases

In patients 1 to 9, the certainty of suspicious lymph nodes increased on PET/CT fusion without altering the clinical nodal staging. In patients 1 and 2, enlarged nodes were seen on md-CT in the paracardial region (patient 1) and near the left gastric artery (patient 2). On side-by-side correlation it was not possible to distinguish whether these nodes were PET positive or not, but fusion revealed FDG-uptake in these nodes. In one patient (3), the lymph nodes were visible on CT at Naruke 4/5 and 17 without FDG accumulation on primary PET review. However, FDG-uptake was noted in two nodes after correction for the difference in height of the diaphragm vault. Only two nodes (Naruke 4/5 and 20) were eventually submitted for pathological examination as resection was abandoned because of tumour invasion in the pericardium (T4 stage). In patient 4, two nodes both > 1 cm (mean 1.6 x 1.1) at Naruke 16, did not show any FDG uptake, indicating a benign enlargement. Fusion revealed that there was indeed nodal FDG-uptake but that it was assimilated by FDG accumulation from the primary tumour. In patient 5, local and distant lymph nodes were detected by CT, as well as skeletal and lung metastases by PET. With precise anatomical correlation, PET/CT fusion could identify exactly the Naruke stations that were involved. Cytological proof was taken only from Naruke 18 and the six month clinical/radiological follow-up was taken as validation. In patients 7 and 8 a small paracardial (patient 6) and para-oesophageal node (patients 7) was missed on CT, although these lesions were suspected on PET and EUS. In patients 8 and 9, PET, CT and EUS did not agree on the localization of

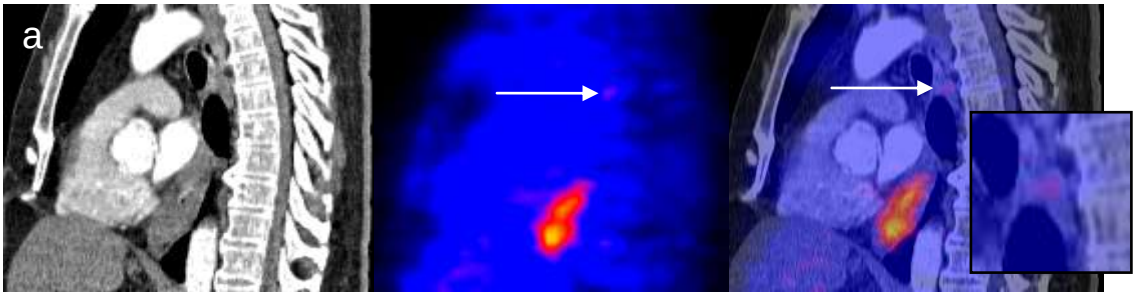
suspected lymph nodes. PET/CT fusion enabled accurate identification and localization in the four nodes.

Number of metastases altered, stage unaltered

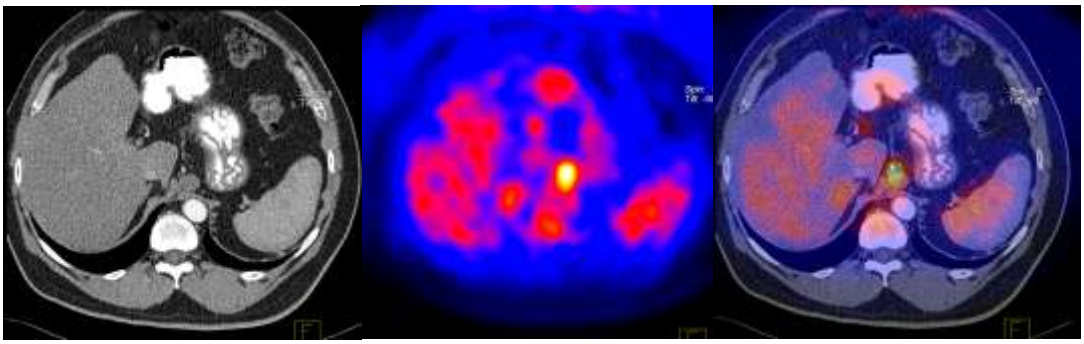
In four patients (10 to 13), the total number of nodal metastases increased as more pathological lymph nodes were observed on PET/CT fusion, though the TNM stage remained unaltered. In patient 10, PET/CT fusion revealed lymph node metastases close to the tumour (Naruke 8 and 16) which were not suspect on CT and were thought to be primary tumour tissue at first PET diagnosis. In patient 12, an initially missed node metastasis at Naruke 16 was detected on PET/CT fusion. Two other enlarged lymph nodes >1 cm at Naruke 8 and 17 did not show any FDG-uptake on visual correlation. In patient 13, no nodal involvement was observed on PET scanning, but on PET/CT fusion there was indeed FDG- uptake in the para-oesophageal lymph nodes.

In one patient (patient 14), the number of metastases decreased. CT detected three lymph nodes > 1 cm, but on side-by-side fusion it was impossible to determine whether these nodes were involved due to their close proximity. PET/CT fusion clearly showed that one of these nodes did not absorb any FDG. Unfortunately, at exploration, pathologically proven cervical metastasis was found and resection was abandoned. Hence, PET/CT findings of enlarged lymph nodes at Naruke 8 were verified by the 12-months follow-up.

Figure 1. Upstaging (a) and downstaging (b)



(a) Patient 15: FDG-PET, low suspicion for both nodal and skeletal metastases, but without suspicion on md-CT or EUS. Software fusion clearly showed metastatic nodal metastasis in the para-oesophageal region. Magnification shows the involved lymph node.



(b) Patient 16: enlarged lymph node in the paracardial region staged as N1 on md-CT. On FDG-PET, FDG-uptake was seen in the celiac region, staged as M1a. After software PET/CT fusion both findings appeared to be the same lesion in the paracardial region.

Altered staging

The TNM classification was altered by PET/CT fusion in 4 patients (patients 15 to 18; 6.6%). Upstaging was found in one patient (15), but had no impact on the resectability. There was a low suspicion on PET for nodal (Naruke 8 and 20) and skeletal metastases, not confirmed by CT or EUS. After software PET/CT fusion pathologically confirmed metastatic lymph nodes were clearly visible at Naruke 8 and 16 (Figure 1a). Downstaging by PET/CT fusion was found in three patients (patient 16, to 18). In patient 16 an enlarged node at Naruke 16 was staged as N1 on

Table 4. Details of the 18 patients with differences in staging between software PET/CT fusion and visual correlation

Pt	*Lpt*	*H*	*S*	*I*	L_{EUS} *(n)*	L_{visu}*(n)*	L_{soft} *(n)*	L_{path} *(n)*
1	Distal	AC	III	2	16, 17 (2)	16 (1)	16 (1)	7,8,16,17 (22)
2	GOJ	AC	III	2	- (0)	17 (1)	17 (1)	17 (3)
3	Distal	SC	III	2	4/5,17 (5)	4/5,17 (10)	4/5,17 (12)	4/5, 20 (2)
4	GOJ	AC	III	2	4/5,7,8,16,	7,8,16 (6)	7,8,16 (6)	8,16 (2)

					17 (8)			
5	Distal	AC	IVA B	2	8,16,18 (4)	8,16,17,18 ,20 (13)	8,16,17,18 ,20 (13)	18 (1)
6	Distal	AC	III	2	16 (1)	4/5,16,17 (7)	4/5,16,17 (7)	-
7	Distal	AC	III	2	8 (1)	8 (1)	8 (1)	8,16 (2)
8	Distal	AC	IVA	2	7, 18 (3)	8,17 (4)	8,17 (4)	8,17 (4)
9	GOJ	AC	IVA	2	20 (3)	17,20 (3)	20 (3)	20 (2)
10	Distal	AC	IIB	3	8 (1)	17 (1)	8,16,17 (3)	8,16,17 (3)
11	Distal	SC	III	3	8 (1)	7 (1)	4/5,7 (2)	4/5,8 (8)
12	GOJ	AC	III	3	16 (3)	19 (1)	19,16 (2)	16 (1)
13	Distal	AC	III	3	8 (1)	- (0)	8 (1)	4,5,8,16
14	Distal	AC	III	4	8 (1)	8 (5)	8 (4)	-
15	Distal	AC	IIA	6	- (0)	- (0)	8, 16 (2)	8, 16, 17
16	Distal	AC	IVA	8	16 (2)	16, 20 (2)	16 (1)	16, 17 (2)
17	Distal	AC	IIA	8	- (0)	4/5, 7 (3)	- (0)	- (0)
18	Distal	AC	III	8	17 (3)	17, 20 (3)	17 (2)	8, 16, 17

L_{pt}: location of primary tumour, GOJ: gastro-oesophageal junction, H: histology, AC: adenocarcinoma, SC: squamous cell carcinoma, S: clinical stage based on staging without PET/CT fusion, I: improvements 2-9: see Table II, L: localization of lymph node station(s) according to Naruke by endoscopic ultrasound (EUS), visual correlation (visu), software fusion (soft) or on pathological examination (path), 4/5:paratracheal, 8: para-oesophageal, 16: paracardial/curv. minor, 17: left gastric artery, 20: celiac trunk, n: number of lymph node metastases.

CT, but as FDG-uptake was visible at the celiac trunk it was staged as M1a. At PET/CT fusion both findings appeared to be the same lesion, staged as N1 (Figure 1b). In patient 17, three lymph nodes > 1 cm were found on CT and during visual correlation it was unclear whether a slightly diffuse accumulation of FDG-uptake was attributable to these nodes or to a Barrett oesophagus segment. PET/CT fusion showed undeniably that these nodes were clear. In patient 18, a suspicious celiac node metastasis (Naruke 20) was noted on visual correlated FDG-PET, but software PET/CT fusion enabled precise localization of increased FDG-uptake at Naruke 17.

Sensitivity, specificity and accuracy

Although not statistically significant (p=0.250), the diagnostic accuracy of PET/CT fusion (87%; 53/61) was slightly better than side-by-side visualization (82%; 50/61) in the assessment of locoregional metastases. Sensitivity and specificity of side-by-side visualization were 80% (12/15) and 83% (38/46), respectively. The sensitivity and specificity of PET/CT fusion in the assessment of nodal metastases were both 87%; 13/15 and 40/46, respectively.

Discussion

This study showed that software-fused PET/CT had a supplementary value over visually correlated FDG-PET and md-CT in the assessment of nodal metastases in 30% of the patients with cancer of the oesophagus. Improved assessment of locoregional tumour foci is necessary for appropriate surgical treatment, but also for more accurately planned target volumes, particularly in the neoadjuvant chemoradiation treatment of these tumours.[29,30] Refinement of the nodal assessment was found by PET/CT fusion compared to the side-by-side visualisation method, even though the N-stage itself was not significantly affected. It is this refinement that is of major importance in radiotherapy planning.

However, there are some potential pitfalls in the interpretation of PET/CT fusion images. Although md-CT has a high accuracy in detecting enlarged lymph nodes, its specificity for metastases is low. Previous studies showed that lymph nodes of > 1 cm on CT without FDG-uptake on PET are usually benign.[23,31,32] Visual correlation between PET and CT is usually sufficient to determine this difference. Therefore, improvements in staging were not taken into account when summarizing improvements of software fusion compared to visual fusion. This statement should be interpreted with caution as it was difficult to visualize the regional lymph nodes near the primary tumour. In many cases, FDG-uptake in the primary tumour may mask nearby lesions, due to the assimilation of FDG-uptake in both. The para-oesophageal and paracardial areas are particularly difficult to interpret in this way. The lymph nodes can be categorized only as benign on the aforementioned criteria when they are not in the proximity of the primary tumour. Software fusion can be helpful in identifying whether these lymph nodes are located near the primary tumour. Another pitfall in the determination of nodal metastases on PET/CT fusion is the difficulty in exact pathological localization. Only meticulous marking during surgery with mapping of all visible or palpable nodes region by region in the resected specimen according to the Japanese method makes correct identification possible.

There are also some inherent difficulties in software PET/CT fusion. Firstly, the outlining in software fusion depends, to a certain extent, on human expertise and appraisal, as does its evaluation. Therefore, small inter-observer variation is inherent to this kind of science.[31] To overcome this problem in the present study, all the fusion images were studied and scored separately by an experienced nuclear physician and a radiologist. Disagreements were solved in a consensus meeting. Secondly, the software-fused images consist of two images from two different techniques at different times. Consequently body posture and position differ between the md-CT and PET. Fortunately, structures close to the spine, like the oesophagus, show only minimal movements and are therefore very suitable for fusion, though the position of the diaphragm often does not match as md-CT is conducted at maximum inspiration and PET during moderate respiration. Therefore, it is difficult to fuse PET and CT images below the vault of the diaphragm. Some authors have reported a failure of 30-39% in software PET/CT fusion of the evaluated cases.[32,33] However, these studies also described an increased success rate if the PET transmission data were incorporated in the fusion process for attenuation correction.

Recently hybrid PET/CT scanners have become available. The use of hybrid scanners partly overcomes these above mentioned limitations because PET and md-CT are performed simultaneously, in the same body posture and nearly at the same diaphragm position. Several studies comparing hybrid PET/CT with visually correlated FDG-PET/CT have reported an improvement of 22-49% in the detection, localization and characterization of malignant lesions with an accuracy of 90-96%.[21-23,34-36] Nevertheless, hybrid FDG-PET/CT scanners still consist of two separate scanners in one combined device, and difficulties may occur in the application of these scanners. The quality of the md-CT scan as part of a hybrid scan is frequently inferior to the quality of a separate md-CT scan, because md-CT is primarily based on anatomical mapping for precise localization of structures for FDG-PET. Additionally, oral contrast fluid is not administered, accurate imaging of pulmonary

and hepatic lesions might be problematic due to respiratory movements and timing for arterial/venous imaging are not optimal. Furthermore, as earlier research has revealed no benefit of FDG-PET in stage I and II disease, hybrid scanning seems to be of limited value compared to md-CT in this group of patients.[37] It is a relatively expensive investigation used in a whole population, while PET scanning will have no additional value in some subgroups.

In conclusion, fusion of FDG-PET and md-CT images improves the detection and/or localization of locoregional metastases in oesophageal cancer cases with a more accurate differentiation between physiological and pathological lesions.

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Chapter 3

Value of EUS in Determining Curative Resectability in Reference to CT and FDG-PET: The Optimal Sequence in Preoperative Staging of Esophageal Cancer?

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Abstract

Background

The separate value of endoscopic ultrasonography (EUS), multidetector computed tomography (CT), and (18)F-fluorodeoxyglucose positron emission tomography (FDG-PET) in the optimal sequence in staging esophageal cancer has not been investigated adequately.

Methods

The staging records of 216 consecutive operable patients with esophageal cancer were reviewed blindly. Different staging strategies were analyzed, and the likelihood ratio (LR) of each module was calculated conditionally on individual patient characteristics. A logistic regression approach was used to determine the most favorable staging strategy.

Results

Initial EUS results were not significantly related to the LRs of initial CT and FDG-PET results. The positive LR (LR+) of EUS-fine-needle aspiration (FNA) was 4, irrespective of CT and FDG-PET outcomes. The LR+ of FDG-PET varied from 13 (negative CT) to 6 (positive CT). The LR+ of CT ranged from 3-4 (negative FDG-PET) to 2-3 (positive FDG-PET). Age, histology, and tumor length had no significant impact on the LRs of the three diagnostic tests.

Conclusions

This study argues in favor of PET/CT rather than EUS as a predictor of curative resectability in esophageal cancer. EUS does not correspond with either CT or FDG-PET. LRs of FDG-PET were substantially different between subgroups of negative and positive CT results and vice versa.

Introduction

Accurate preoperative staging in esophageal cancer is important in the choice of treatment, preventing unnecessary toxic preoperative chemoradiation and/or surgical explorations. Moreover, it is essential to determine optimal treatment and to monitor treatment response after neoadjuvant therapy.[1-3] Radical surgery with curative intent is only possible if distant metastases (M1) and infiltration of the primary tumor into adjacent vital structures (T4b) are absent. If present, primary (chemo)radiation, brachytherapy or stent placement are more adequate and less invasive alternatives as palliative treatment.[4-7] Currently, preoperative staging of esophageal cancer includes endoscopic ultrasonography (EUS) with or without fine-needle aspiration (FNA) of suspicious lymph nodes, 16–64 multidetector/slice computed tomography (CT), external ultrasound (US) of the cervical region, and bronchoscopic examination, if indicated, in mid/upper thoracic tumors. To detect distant nodal and systemic metastases, whole-body positron emission tomography with ^{18}F-fluordeoxyglucose (FDG-PET) or PET/CT is widely used.[3] These staging methods are used in different sequences, according to the guidelines employed. Despite these dedicated staging techniques, surgical resection is still abandoned in 10–50% of all cases due to excessive locoregional tumor extent or presence of distant metastases.[3,8]

Assessment of resectability is based on both local and distant criteria. Imaging techniques are more or less complementary, but outcome may also depend on the sequence of the preoperative workup. Furthermore, a recent study showed significant but small differences in perceived patient burden between PET and CT compared with EUS.[9] Therefore, it is important to know the adequate sequences of these different diagnostic methods and when to use PET/CT or only CT (upfront), followed by EUS, and vice versa. Several studies found that FDG-PET combined with EUS-FNA improved preoperative staging of esophageal cancer.[3, 10-13] Fusion of FDG-PET and CT images also provided an increase in

preoperative management from 6 to 25%.[14-16] The optimal staging strategy, however, remains unclear, and the additional value of combined PET/CT has not been determined adequately yet.

Therefore, we used a logistic regression approach to determine the extent to which the individual value of each diagnostic staging technique depends on the order in which the procedure is applied and to determine if this staging method adds useful information to what is already known, either because of individual characteristics or on the basis of preliminary staging results.[17] Three routine diagnostic staging techniques (EUS, CT, and FDG-PET) were tested in terms of curatively intended resectability of esophageal cancer. For this purpose, we compared the likelihood ratios (LRs) in different staging strategies, calculated at the level of the individual patient.

Patients and Methods

Study Design

The medical records from a multicenter (Academic Medical Center, Amsterdam and University Medical Center, Groningen) prospective cohort staging improvement study lasting from October 2002 to October 2004 were used.[18] The study consisted of 258 consecutive patients with biopsy-proven cancer of the thoracic esophagus or gastroesophageal junction (GEJ). Exclusion criteria were age <18 years, inability to undergo major surgery, pregnancy, and history of another malignancy in the previous 5 years. According to the above-mentioned criteria, 216 operable patients were eligible for participation. Informed consent was obtained from all 216 patients who formed our study population. Patient and tumor characteristics are listed in Table 1.

All these patients underwent thoracic and abdominal CT, EUS with FNA on indication, and whole-body FDG-PET within a time period of 6 weeks. All PET/CT and EUS were performed and reviewed independently by well-trained and experienced investigators in both highly qualified centers. Interpretation of each modality was blinded, and investigators were unaware of other clinical or diagnostic data.[18] Resectability was determined by local tumor invasion of vital structures, excluding non-curatively resectable group of unresectable tumor (T4b), unresectable conglomerate of nonregional nodal disease, or distant metastases (M1). Distant metastases included lymph node metastases in the cervical area or at the celiac axis depending upon primary tumor location or hematogenous metastases, usually to liver and lungs and bone metastasis. To exclude pathological cervical lymph nodes, external ultrasonography of the neck with FNA was performed on indication. All potential sites of incurable disease were confirmed pathologically or were followed with additional imaging during at least 12 months. All records, including histology achieved from biopsy, surgical explorations, and resections were registered and available for analysis.

Pathological confirmation or any progression of unconfirmed suspicious lesion during 6-month follow-up was considered as gold standard.

Table 1. Clinicopathological characteristics and univariate analysis of coefficients

	N=216	*%*	*Resectable (n=150)*	*Unsesectable (n=66)*	*p-Value*
Gender					
Male	181	83.8	84.7%	81.8%	0.60
Female	35	16.2			
Age (years)					0.11
Median (range)	63	29-82	63.4 (9.26)	61.17 (10.05)	
Localization[a]					0.14
High	23	10.6	12 (8.0%)	11 (16.7%)	
Low	139	64.4	101 (67.3%)	38 (56.6%)	
GEJ	54	25.0	37 (24.7%)	17 (25.8%)	
Tumor length (cm)					0.001
Median (range)	5.0	0-18	5.47	7.36	
Histological type					0.058
AC	168	77.8	122 (81.3%)	46 (69.7%)	
SCC	48	22.2	28 (18.7%)	20 (30.3%)	
Test outcomes					
EUS outcome	U		2 (1.3%)	8 (12.1%)	n.a.
CT outcome	U		9 (6.0%)	26 (39.4%)	n.a.
FGD-PET outcome	U		5 (3.3%)	30 (45.5%)	n.a.
Clinical stage					
T1	9	4.2			
T2	22	10.4			
T3	171	80.7			
T4	10	4.7			
Missing value	4	-			

Staging based on total staging (EUS-FNA, CT, FDG-PET, and additional investigations, such as external sonography of the neck and bronchoscopy). GEJ: gastroesophageal junction, tumor length: length of the tumor on EUS, AC: adenocarcinoma, SCC: squamous cell carcinoma, MWU: Mann–Whitney U-test, χ^2: Pearson chi-square test, grouping variable: irresectability. [a] High: above the carina, Low: below the carina, U: unresectable.

Computed Tomography

A 16 or 64 multidetector row spiral CT scanner (Philips MX 8000; Philips Medical Systems, Best, The Netherlands or Somatom Sensation; Siemens Medical Systems, Erlangen, Germany) was used for CT imaging. CT scans (collimation 16 × 1.5 mm) were performed with both intravenous and oral contrast fluid and achieved in craniocaudal direction from the neck to the upper abdomen including the liver. Images had 3 mm reconstructed slice thickness with 1.5 mm effective section thickness. Round lymph nodes with low attenuation and lymph nodes with a size cutoff of 10 mm in smallest diameter were suspected to be pathologic.

Endoscopic Ultrasound

EUS was performed with a radial scanner (GF-UM 130 or GF-UM160, 5–20 MHz; Olympus Medical Systems, Tokyo, Japan), and EUS-guided FNA of suspected lymph nodes was obtained via a separate linear-array echoendoscope (GIF-UC140P; Olympus Medical Systems, Tokyo, Japan or FGUX-36, 5–7.5 MHz; Pentax, Benelux, Breda, The Netherlands). A 22-gauge needle was used for aspiration (Echo tip; Wilson-Cook Medical Inc., Winston-Salem, NC). If passage of a standard echoendoscope was not feasible because of stenosis, a small-caliber probe (MH-908, 7.5 MHz; Olympus Medical Systems, Tokyo, Japan) was used in an attempt to pass the tumor. EUS was performed with the patient in left decubitus position under sedation using 2.5–10 mg midazolam intravenously.

Positron Emission Tomography with ^{18}F-Fluorodeoxyglucose

All patients were fasted for at least 4 h before FDG-PET imaging. FDG-PET was performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA). Depending on body weight, a mean dose of 400–580 MBq FDG was administered intravenously. Data acquisition started in whole-body mode 90 min after injection, for 5 min per bed position from the skull to the mid femur.

Statistical Analyses

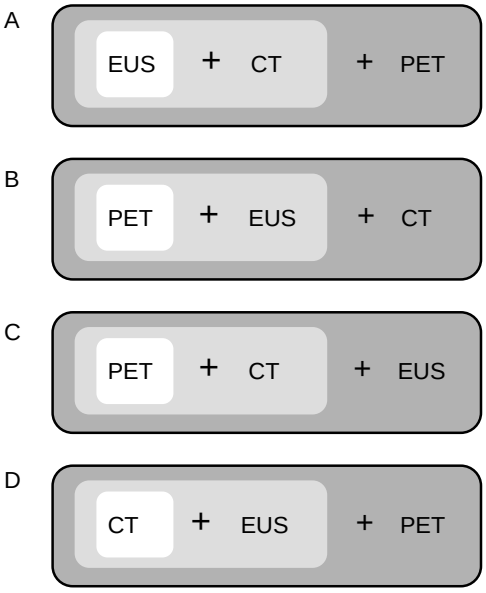
The results of EUS, CT, and FDG-PET together with the results of surgical exploration and pathological evaluation of the resection specimen were converted into a final gold-standard dichotomous outcome: resectable with curative intent ("resectable" hereinafter), or incurable/unresectable. Baseline variables were divided into three groups: (1) individual patient characteristics including age and gender, (2) tumor characteristics of the primary tumor including histological type, location, and length measured on EUS, and (3) staging characteristics including EUS outcome, CT outcome, and FDG-PET outcome. Resectable and unresectable tumors were compared by using the Pearson chi-square test (χ^2) for ordinal/nominal variables and the Mann–Whitney U-test (MWU) for continuous variables.

To estimate the probability of curative surgery (resectable) versus palliative treatment (unresectable), logistic regression analyses were used according to a recently developed regression approach.[17] In this approach, the regression equation for the likelihood ratio (LR) of the test results (logistic regression model) is obtained by taking the difference in coefficients between prior and posterior odds. The prior odds model included all covariates that were significantly related to the resectability of the esophageal malignancy. The posterior odds model included all variables from the prior odds model plus the results of one or two of the additional imaging tests. In this way, the LR of a

resectable tumor is calculated for individual risk profiles. In the conventional log-odds formulation of the Bayes rule, the natural logarithm (ln) of LR is the difference between ln(posterior odds) and ln(prior odds).[17,19] Although we performed regression analyses for the three diagnostic imaging modalities in various sequences, only the four scenarios which are clinically relevant are presented (Figure 1, order A to D).

Descriptive statistics were obtained using SPSS 14.0 for Windows. The multivariable logistic regression analyses for prior and posterior odds models and the LR were programmed in S-PLUS (V6; Insightful Corp., Seattle, WA). Values of p less than 0.05 were considered statistically significant.

Figure 1. Order A to D; four different staging scenarios



White box: one method: first staging procedure,
Grey box: second method: two staging procedures,
Dark grey: third method: three staging procedures.

Results

The length of the tumor was a statistically significant risk factor for irresectability ($p = 0.001$). Not surprisingly, all staging characteristics were also significantly related with curative resectability. Age, gender, tumor location, and histological type were not significantly correlated with curative resection (Table 1). For each scenario (Figure 1, order A to D), the coefficients of the ln(prior odds), ln(posterior odds), and ln(LR) regression models are presented in Table 2. Age, histological type, and tumor length did not significantly contribute to the LRs of the involved diagnostic tests in any of the models ($p > 0.05$).

Impact of Different Staging Tests in Different Staging Scenarios

Figure 2 illustrates the difference a test outcome (Figure 2a, 2b and 2c) and histological type (Figure 2d) made on the LR+ of a following test. We chose tumor length as the X-variable only to spread out our dot plot rather than because of its correlation with the outcomes of the investigated modalities. In Figure 2a and 2b, there is a significant difference between negative and positive outcomes of the preceding test. In Figure 2c, the effect of EUS after PET or CT is not significant, although there is a tendency towards a visually apparent clustering into four groups. This is based on the combination of positive/negative CT results and histological type (adenocarcinoma/squamous cell carcinoma; Figure 2d).

In Table 2, the outcomes of EUS were not significantly related with either the LRs of the CT results or with the LRs of the FDG-PET results (order A; $p = 0.49$ and $p = 0.91$, respectively). CT results were strongly related to the LRs of the FDG-PET results (Table 2, order A; $p = 0.03$). The negative regression

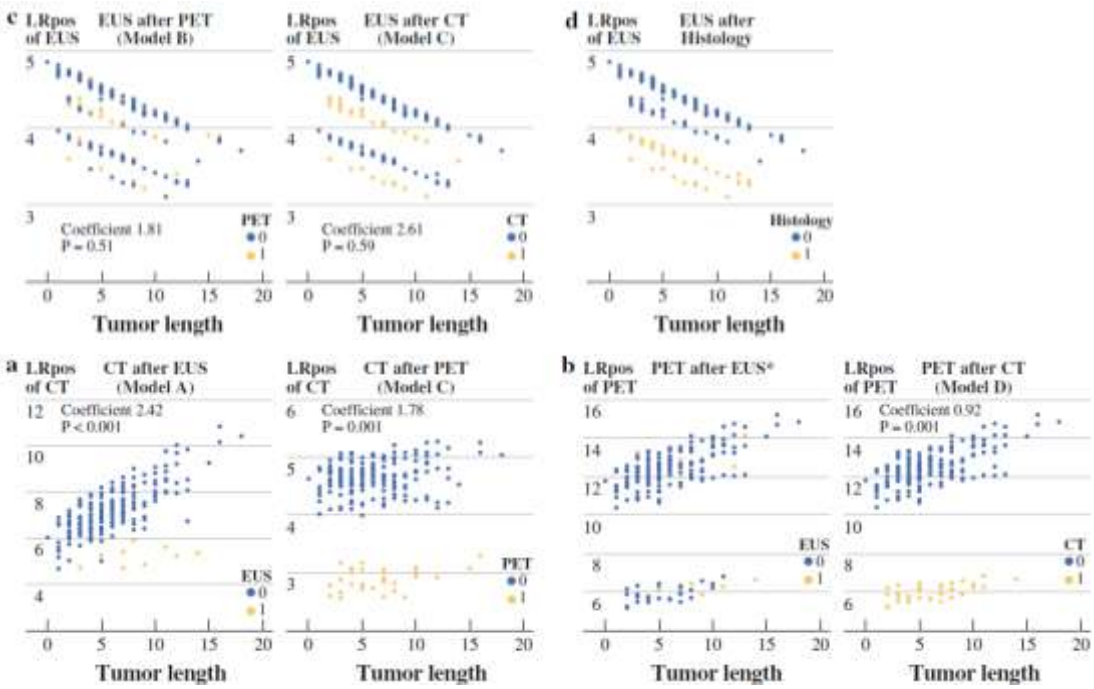
Table 2. Logistic regression models for the likelihood ratio of CT, FDG-PET, and EUS conditional on age, tumor length, and histological type

Stage	*Test*	*Covariate*	*Logistic regression*			*Likelyhood ratio*		
			Coeff	*SE*	*p*	*Coeff*	*SE*	*p*
Order A: EUS – CT – FDG-PET								
I	EUS	–	1.79	0.86	0.04	–	–	–
II		EUS	1.42	0.97	0.14	-0.37	0.53	0.49
	CT		2.42	0.46	<0.001	2.42	0.60	<0.001
III		EUS	1.48	1.01	0.14	0.06	0.53	0.91
		CT	1.69	0.53	0.001	-0.73	0.33	0.03
	FDG-PET		2.91	0.57	<0.001	2.91	0.92	0.001
Order B: FDG-PET – EUS – CT								
I	FDG-PET	–	3.37	0.55	<0.001	–	–	–
II		FDG-PET	3.36	0.55	<0.001	-0.01	0.07	0.95
	EUS		1.81	0.93	0.05	1.81	2.73	0.51
III		FDG-PET	2.91	0.57	<0.001	-0.45	0.19	0.02
		EUS	1.48	1.01	0.14	-0.33	0.49	0.50
	CT		1.69	0.53	0.001	1.69	0.65	0.01
Order C: FDG-PET – CT – EUS								
I	FDG-PET	–	3.37	0.55	<0.001	–	–	–
II		FDG-PET	2.90	0.57	<0.001	-0.46	0.19	0.01
	CT		1.78	0.52	0.001	1.78	0.54	0.001
III		FDG-PET	2.91	0.57	<0.001	0.01	0.10	0.92
		CT	1.69	0.53	0.001	-0.08	0.11	0.45
	EUS		1.48	1.01	0.14	1.48	2.62	0.57
Order D: CT – EUS – FDGPET								
I	CT	–	2.47	0.45	<0.001	–	–	–
II		CT	2.42	0.46	<0.001	0.05	0.06	0.44
	EUS		1.42	0.97	0.14	1.42	2.61	0.59
III		CT	1.69	0.53	0.03	-0.73	0.33	0.03
		EUS	1.48	1.01	0.14	0.06	0.53	0.91
	FDG-PET		2.91	0.92	0.001	2.91	0.92	0.001

Coeff: coefficient, SE: standard error, p: *p*-value, I: one and first staging procedure, II: second method/two staging procedures, III: third method/three staging procedures

coefficient for CT (Table 2, order D; coeff. = −0.73) indicates that LR+ and LR− of FDG-PET were lower when CT was also positive compared with negative CT findings. Vice versa, FDG-PET results were strongly related with the LRs of CT (Table 2, model C; $p = 0.01$). EUS had no impact as a test for incurability, if it was performed after FDG-PET and CT in the staging workup (Table 2, order C; $p = 0.57$), nor was there a significant relation between FDG-PET + CT results and the LRs of EUS (Table 2, order C; $p = 0.92$ and $p = 0.45$, respectively). There was also no significant relation between FDG-PET imaging and the LRs of EUS-FNA (Table 2, order B; $p = 0.95$). However, in the workup with FDG-PET and EUS-FNA, PET was strongly related to the LRs of CT imaging, but EUS-FNA was not (Table 2, order B; $p = 0.02$ and $p = 0.50$, respectively).

Figure 2. Positive likelihood ratio of CT, FDG-PET and EUS conditional on tumor length (a to c) and on histological cell type (d) stratified to negative and positive test results of both other tests.



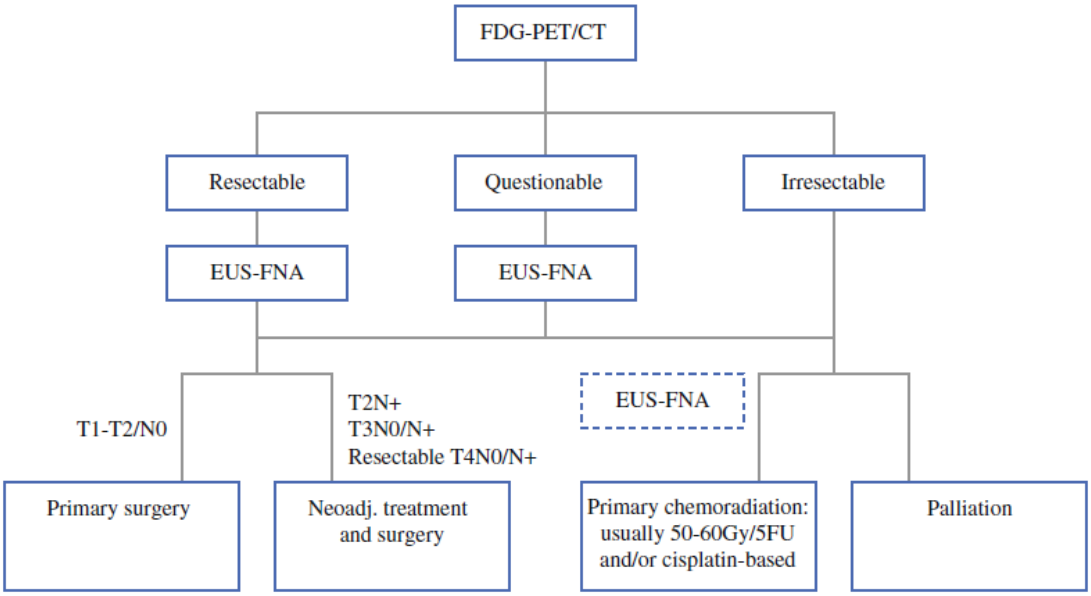
Results were not corrected for the effects of the third test because in these models there was no third test as co-variable. Test outcome 0: resectable with curative intent, 1: incurable/unresectable disease. Histology 1: adenocarcinoma, 2: squamous cell carcinoma.

Optimal Preoperative Workup

In Figure 1, it is already obvious that a staging scenario with a PET scan upfront followed by CT and EUS will yield the highest ratio of true-negative test outcomes of all one- and two-step strategies.

According to all of the above-described models, we composed an idealized protocol for optimal staging workup using EUS, CT, and FDG-PET on split levels for patients with clearly resectable, questionably resectable, and irresectable esophageal tumors (Figure 3). In this flowchart, we recommend performance of PET/CT upfront in every patient, followed by EUS in those with clearly resectable disease to identify patients with locally advanced disease, as they may benefit from neoadjuvant chemoradiation before surgery. When there is disagreement about resectability with curative intent based on the location of suspect lymph nodes or because of tumor depth, we advise EUS-FNA for pathological examination of FDG-avid sites and/or suspicious lesions on PET/CT imaging in advanced, questionably resectable disease. In patients with primary irresectable disease that could possibly be managed curatively by definitive chemoradiation, EUS-FNA should be performed on indication. However, EUS can be omitted in patients with clearly incurable disease, so they can be referred immediately for palliative treatment.

Figure 3 Flowchart illustrating optimal staging protocol for patients with esophageal cancer on split levels for clearly resectable, questionably resectable, and irresectable esophageal tumors. 5FU 5-fluorouracil



Discussion

In this study a validated reformulated logistic regression approach was used to calculate the likelihood ratios of CT, FDG-PET, and EUS in order to determine the resectability with curative intent for different patient, tumor, and staging characteristics.[17] Given the outcomes of one or two diagnostic tests, we were able to determine the value added by each test in the staging workup of esophageal cancer patients in predicting a dichotomous outcome (curative resectability versus irresectability). It was not possible to make subdivisions based on age, histological type, or tumor length in deciding whether to perform a test or not.

According to the results of this logistic regression approach, PET/CT has to be recommended as the first staging procedure, reserving EUS for limited cases and candidates with curable disease (Figure 3). CT and FDG-PET outcomes strongly overlap and strengthen each other. FDG-PET reaches the highest LR+ when CT is negative (LR+ = 12.5–13.0), and vice versa the LR+ of CT reaches 4.4. EUS is insensitive with respect to resectability, with nonsignificant LRs when the results are expressed as a dichotomous outcome. This finding is not in line with the generally allotted role of EUS in esophageal cancer staging. One explanation might be that criteria based on nodal status and depth of tumor invasion alone are not strong enough to preclude surgical resection. Even though EUS is a powerful test for detecting lymph node metastases and tumor depth, these outcomes have almost no influence on decision-making when incurability/irresectability is the only parameter to be assessed. Only when EUS clearly identifies patients with a T4b tumor or cytologically proven nonregional nodes is it helpful for the exclusion of patients from potentially curative surgery. In the current study, only ten tumors (10/216; 5%) were considered as not curatively resectable on EUS as they were staged as T4b tumors. Usually the endoscopist will stage a tumor as T4 if he or she is clearly convinced of tumor invasion into surrounding structures precluding radical surgery. However, if

invasion is not clear or is doubtful, the tumor will probably be staged as T3 and the patient, in most cases, will be offered neoadjuvant therapy as standard treatment. Based on these results, EUS has limited impact beyond PET/CT on staging advanced esophageal tumors in terms of curative resectability. EUS seems to be more valuable as an additional long-term prognostic factor rather than a potential predictor of irresectability at time of diagnosis.

Currently, neoadjuvant chemoradiation is being increasingly applied in the treatment of locally advanced esophageal cancer in an effort to improve microscopic radical resectability and survival by downstaging the tumor process and reducing local recurrence rates. In this way, staging has major consequences on treatment selection and also when comparing outcomes between studies and institutes. Furthermore, EUS is an invasive diagnostic procedure and not always applicable because of stenosis or use of a less accurate miniprobe in up to 30% of cases, which may lead to inadequate assessment of depth invasion and nodal staging.[20] Moreover, in a previous study the perceived patient burden of EUS in assessment of the preoperative tumor stage was relatively high compared with CT and or PET/CT. Both EUS and FDG-PET have relatively good accuracy in restaging esophageal cancer after neoadjuvant therapy. Although both imaging methods have their limitations in assessing response to neoadjuvant chemoradiation, the accuracy rate of CT alone is poor.[21]

The more tests used in a preoperative staging program, the higher the chance of a correct outcome. However, one must balance likelihoods and certitude against costs, radiation, and inconvenience for the patient. Difficulties arise when test outcomes are contradictory. This study offers a new perspective on the performance of current diagnostic tests in the staging workup for esophageal cancer patients. It indicates the individual impact of each test on medical decision-making and the congruence between them. These results strongly argue for use of PET/CT as the first staging procedure, reserving EUS-FNA for

those cases with uncertainty or disagreement about the location of positive lymph nodes (regional versus nonregional nodes) or tumor depth, which may affect curative resectability. Biopsies of FDG-avid sites at time of EUS will actually increase the yield of pathological proof from initial EUS without scheduling a separate EUS to prove irresectable disease.

Acknowledgment

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Part III

FDG-PET/CT in Radiotherapy Planning

Chapter 4

Impact of 18-fluorodeoxyglucose positron emission tomography on computed tomography defined target volumes in radiation treatment planning of oesophageal cancer: Reduction in geographic misses with equal inter-observer variability

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Abstract

Background

Target volume definition in modern radiotherapy is based on planning computed tomography (CT). So far, 18-fluorodeoxyglucose positron emission tomography (FDG-PET) has not been included in planning modality in volume definition of esophageal cancer. This study evaluates fusion of FDG-PET and CT in patients with esophageal cancer in terms of geographic misses and inter-observer variability in volume definition.

Patients and Methods

In 28 esophageal cancer patients, gross, clinical and planning tumor volumes (GTV; CTV; PTV) were defined on planning CT by three radiation oncologists. After software-based positron emission tomography and computed tomography (PET/CT) fusion, tumor delineations were redefined by the same radiation-oncologists. Concordance indexes (CCI's) for CT and PET/CT based GTV, CTV and PTV were calculated for each pair of observers.

Results

Incorporation of PET/CT modified tumor delineation in 17/28 subjects (61%) in cranial and/or caudal direction. Mean concordance indexes for CT-based CTV and PTV were 72 (55–86)% and 77 (61–88)%, respectively, vs. 72 (47–99)% and 76 (54–87)% for PET/CT-based CTV and PTV. Paired analyses showed no significant difference in CCI between CT and PET/CT.

Conclusions

Combining FDG-PET and CT may improve target volume definition with less geographic misses, but without significant effects on inter-observer variability in esophageal cancer.

Introduction

In the treatment of esophageal cancer, radiotherapy is commonly used in combination with chemotherapy as neo-adjuvant treatment prior to surgery. Since there is no evidence of a survival benefit for patients getting surgery after chemoradiation compared with patients with chemoradiotherapy alone, it should be considered a valid alternative for treatment of esophageal cancer, especially in patients not fit enough for extensive surgery.1–3

Currently, modern radiotherapy includes target volume definition based on planning computed tomography (CT) scan. Target volume definition includes delineation of the gross tumor volume (GTV, i.e., the primary tumor and lymph node metastases); the clinical target volume (CTV, i.e., the GTV plus a safety margin in all directions and the elective nodal areas to cover potential microscopic disease); and planning target volume (PTV) to account for set-up inaccuracies and esophageal, cardiac and respiratory movements during radiation.

Until now, planning-CT based target volume definition is considered the gold standard. Limited depiction of pathologic changes in normal-sized structures and intrinsic lack of contrast between soft tissues may result in inter-observer variability in target volume delineation. Also, cranial and caudal tumor delineation can be complicated when the esophageal lumen has collapsed or the stomach is not totally expanded.4

Recently, applied dual-modality 18-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) might have advantages to determine the GTV and the extent of its motion in several directions, as PET/CT imaging improves by reducing the PET scan time considerably from 45 to 60 min to 10–20 min for PET/CT using CT for attenuation correction.5 By combining two complementary techniques into one new imaging device, functional abnormalities can be visualized with high accuracy and facilitates the differentiation between physiological and pathological uptake, reducing the

incidence of both false positive and false negative outcomes.6–8 Therefore, PET/CT may play an important role in increasing the accuracy of tumor delineation and clinical outcome after radiotherapy. In several studies, PET/CT has a significant impact on the GTV, CTV and PTV and may result in a reduction of radiation-induced toxicity and improvement of loco-regional tumor control.9

The current study was initiated to test the hypothesis that the addition of FDG-PET to planning-CT results in a more accurate radiation planning with less inter-observer variability in the delineation of the GTV among patients with esophageal cancer as compared with planning-CT alone.

Patients and methods

This study is a retrospective radiotherapy (RT) planning study that utilizes diagnostic CT and FDG-PET images of patients with esophageal cancer from a prospective surgical study that looked at FDG-PET for staging. All patients had given informed consent and were entered between October 2002 and August 2004. They were staged by endoscopic ultrasonography (EUS), cervical/thoracic/abdominal CT, whole body FDG-PET, external ultrasound (US) of the neck, and fine needle aspiration biopsy (FNAB) or other additional investigations on indication. Tumors were staged according to the latest tumor-node-metastasis (TMN) system of the Union Internationale Contre le Cancer (UICC).10 Lymph node metastases within 1 cm of the celiac trunk were classified as M1a in case of distal esophageal cancer and as M1b in case of mid- or proximal esophageal cancer. Cervical metastases were graded as M1a in case of proximal cancer and as M1b when the tumor was located in the mid- or distal esophagus. Suspicious lymph nodes were verified by cytological or histological examination or otherwise by 12 months of radiological and clinical follow-up if pathological examination was not possible.

Patients

Eligible patients presented with a curatively resectable tumor, except for T1N0, of the thoracic esophagus. Patients with non-resectable T4 tumors invading into vital structures or with distant metastases (M1b), either lymphatic or hematogenous, were excluded from this study. Also excluded were patients who underwent recent thoracic surgery and/or stent placement. Twenty-eight patients fulfilled the eligibility criteria and were included in the study. The median age was 63 years (range: 48–80). Patient and tumor characteristics are listed in Table 1.

Table 1. Patient characteristics

Characteristics	*n = 28 (%)*
Sex	
Male	23 (82)
Female	5 (18)
Age (years)	
Mean (range)	63
Range	48 - 80
Histology	
AC	24 (86)
SC	4 (14)
Localization	
High	3 (11)
Low	21 (75)
GEJ	4 (14)
Clinical stage	
T2N0M0	4 (14)
T2N1M0	1 (4)
T3N0M0	8 (29)
T3N1M0	12 (43)
T3N1M1a	2 (7)
T4N1M0	1 (4)

AC, adenocarcinoma; clinical stage, staging based on clinical examination, endoscopic ultrasound, computed tomography, positron emission tomography, additional investigations when necessary but without FDG-PET/CT fusion; GEJ, gastroesophageal junction; SC, squamous cell carcinoma.

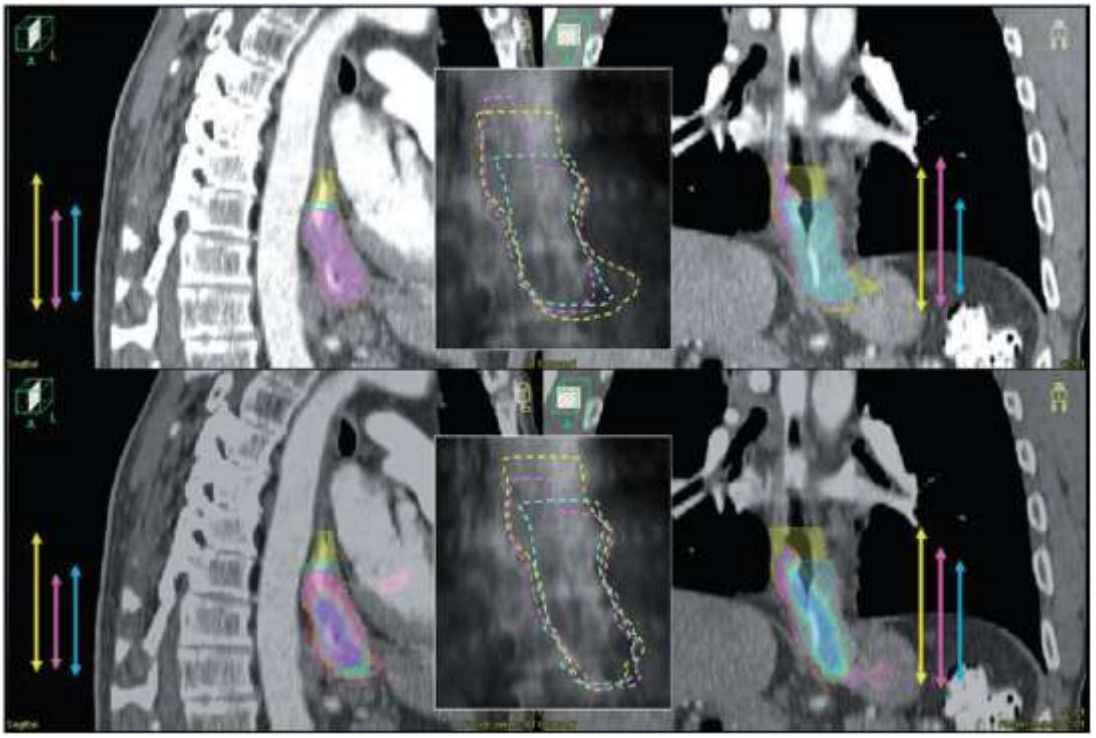
Imaging protocol

CT scans and whole body FDG-PET scans were performed within 2 weeks after the initial diagnosis. CT scans were performed with a 16 or 64 multidetector row spiral CT scanner (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). Patients had to drink 500 mL of oral contrast fluid directly before the scanning process. CT scans were obtained in cranial-caudal direction from the lower neck to the upper abdomen, including the liver, 70–90 seconds after an intravenous injection of 120 mL iodixanol contrast (Vispaque, GE Healthcare

Worldwide, Buckinghamshire, UK). Arms were positioned upward above the head and the examination was performed at maximal inspiration. Image slices had a 3-mm reconstructed thickness with a 1.5-mm effective section thickness (collimation 16 × 1.5 mm). Lymph nodes measuring 10 mm or more were considered malignant as well as round hypo-dense lymph nodes measuring >5 mm.

FDG-PET scans were performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA). The 951/31 acquires 31 planes over 10.9 cm, while the HR+ acquires 63 planes over a 15.8 cm axial field of view. Patients had to fast for at least 4 hours before 190–810 MBq FDG (mean dose 396 MBq, s.e. 7.5 MBq, depending on body weight) was administered intravenously. Ninety minutes after contrast injection, emission scans were performed for 5 min per bed position from the skull base to mid-femur, arms beside the body. Transmission scans were performed for 3 min per bed position allowing attenuation correction. Scans were corrected for decay, scatter and randoms, while ordered subset expected maximization (OSEM) with two iterations and 16 subsets was used for reconstruction. A Gaussian filter of 5 mm full width at half maximum was used for post smoothing of the reconstructed images.11 FDG-uptake was scored by two nuclear medicine physicians on a four-point scale of intensity: 'normal' (physiological), 'slightly increased,"moderate increased' and 'intense increased.' Interpretation of intensity was scored on a five-point scale: 'absolutely benign,"probable benign,"indeterminate,"probably malignant' and 'definitely malignant.' All 'indeterminate,"probably malignant' and 'definitely malignant' lesions were defined as hotspot. Suspect lesions (scores 3–5) were verified by FNAB, pathological examination during or after surgery, or otherwise by radiological and clinical follow-up to one year.

Figure 1. Sagittal and coronal cross-sections of a tumor located at the gastro-esophageal junction



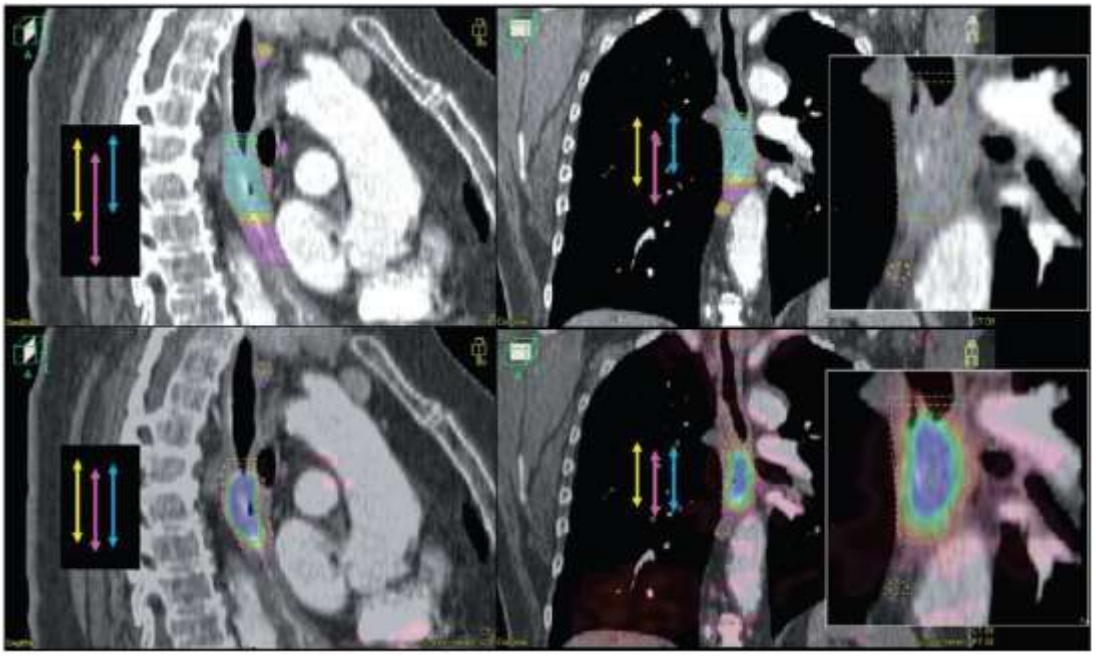
Especially the tumor's extension into the stomach is vague. PET/CT imaging decreased the inter-observer variability (Patient 6; mean CCI of CT-GTV: 57% vs. mean CCI of PET/CT-avid GTV: 64%). Left-side: sagittal cross-sections; right-side: coronal cross-sections; on top: CT-images; beneath: PET/CT images; in the middle: transmission scans with CT structures (above) and PET/CT-avid structures (below); pink and blue and yellow structures: three different delineations of three different observers.

Data interpretation and analyses

Cervical/thoracic/abdominal CT images were reviewed by two experienced radiologists and FDG-PET images were reviewed independently by two experienced nuclear physicians. The GTVs of the primary tumor (GTV-pt) and suspicious lymph nodes (GTV-ln) visible on CT were defined independently and blinded to each other by three experienced radiation-oncologists (observers A, B and C), using additional information of the EUS (including tumor length, location, extension, and suspicious nodes) FNAB, physical examination and knowledge of clinical tumor behavior. The CTV was defined as the CTVs of the

primary tumor (CTV-pt) and lymph node metastases (CTV-ln) as far as they did not overlap each other. The CTV-pt was delineated as the GTV-pt plus a margin of 10 mm in the transversal plane and a 20-mm margin in caudal direction if the tumor was expanded into the stomach or otherwise a 30 mm margin in cranial-caudal direction, following the curves of esophagus with exclusion of bony structures. For lymph nodes, a 10-mm margin in the whole circumference in the transversal plane was added to the GTV-ln. The PTV was automatically generated by adding a 3D-margin of 10 mm around the CTV.

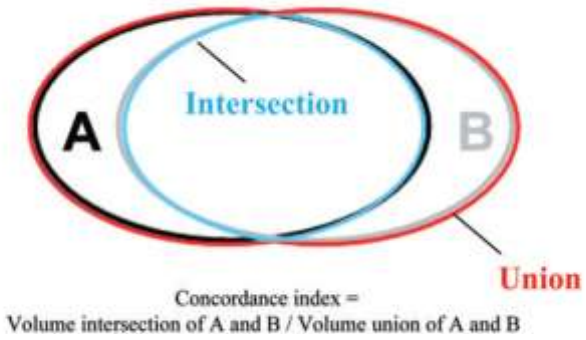
Figure 2. Sagittal and coronal cross-sections of a tumor located in the distal part of the esophagus, with major differences in cranial-caudal delineation



Incorporation of FDG-PET imaging decreased both tumor length and inter-observer variability (Patient 10; mean CCI of CT-GTV: 56%, vs. mean CCI of PET/CT-avid GTV: 76%, tumor length on CT: 52 mm vs. 48 mm on PET/CT). Left-side: sagittal cross-sections; right-side: coronal cross-sections with enlargements of the tumor delineations; on top: CT-images, beneath: PET/CT images, coronal images of the CT structures (above) and PET/CT-avid structures (below); yellow, pink and blue structures: three different delineations of three different observers.

Software-based PET/CT fusion was accomplished on a Siemens Workstation using the Oncentra MasterPlan software program. An experienced physician carried out or supervised the fusion process. To differentiate tumor from normal tissue, we did not estimate a rigid standard uptake value (SUV), but we used the method which is described as superior by Nestle.12 In this method, FDG-uptake in the liver tissue is used as reference tissue for FDG-uptake under fasting conditions. The diameter of an FDG hot spot consisted with the CT tumor diameter on one slice with maximal tumor size. After software-based PET/CT fusion, tumor delineations were redefined independently and blinded by the same radiation oncologists (Figures 1 and 2).

Figure 3. Concordance index



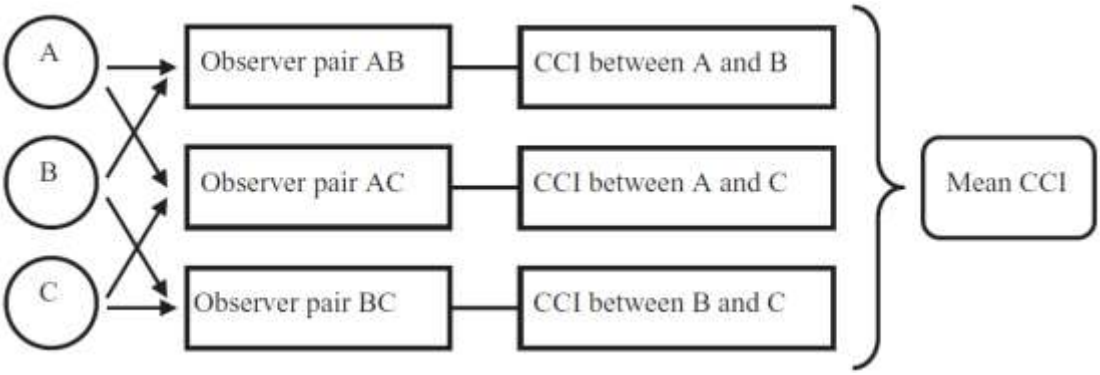
A: volume delineated by observer A (grey**),** B: volume delineated by observer B (black)**,** Volume intersection (blue), volume union (red)

The length of the esophageal tumor was measured in cranial-caudal direction both on CT and PET/CT by all three observers. Mean tumor length and target volumes were calculated per patient for statistical analysis. Volume intersections (Vi) and volume unions (Vu) of GTV, CTV and PTV were calculated for all three pairs of observers. Inter-observer concordance indexes (CCI) were computed by dividing the Vi of one observer pair by the Vu of that observer pair (Figure 3). Mean CCIs were calculated per subject. These calculations were executed for both

CT-based volumes and PET/CT based volumes. Finally, the volume intersections of CT and PET/CT-based GTV, CTV and PTV were calculated per observer. With this, the volume percentages of PET/CT-avid target volumes situated outside the CT volumes were computed by dividing the PET/CT volumes by the volume intersections of CT and PET/CT volumes. These percentages were also averaged per patient (Figure 4).

Both target volumes and CCIs in CT and PET/CT-based target volume definition were compared in nonparametric paired analysis using the Wilcoxon test. *P*-values <0.05 were considered statistically significant (SPSS 16.0 for Windows).

Figure 4. Stream flow per patient



CCI, concordance index. The mean CCI was calculated from the CCIs of all three observer pairs. This was done for both CT and PET/CT-based target volume definition.

Results

Tumor length and target volumes

The mean tumor length on CT was 58.1 mm (range: 18.0–97.5; 95% CI: 49.9–66.4) vs. 57.1 mm (range: 33.0–99.7; 95% CI: 50.0–64.2) on PET/CT. In 15 out of 28 patients (54%), the mean observed PET/CT-based tumor length was significantly smaller than the mean observed CT-based length (mean decrease in tumor length: 7.2 mm; P= 0.001), and in nine cases it was significantly larger (mean increase in tumor length: 9.2 mm; P= 0.008). However, these changes by PET/CT were not significant when decreases and increases in tumor length were taken together (P= 0.639). The mean difference between CT and PET/CT-avid tumor length was 1.1 mm (range: −24.0–27.0).

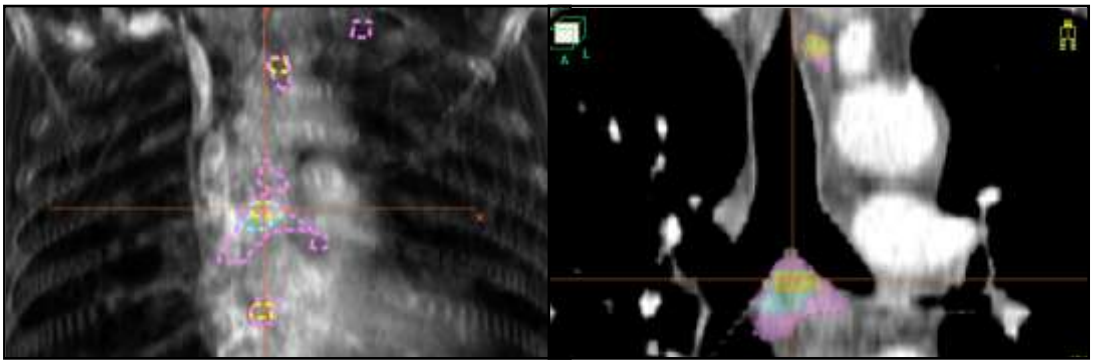
The mean GTV-pt increased after PET/CT fusion from 46.2 cm3 (range: 4.8–116.5; 95% CI: 34.4–58.0 cm3, Table 2) to 48.8 cm3 (range: 8.1–138.0; 95% CI: 36.1–61.6 cm3), which was not statistically significant (P= 0.785). In 11 out of 28 patients (39%), FDG-PET information led to an increase in the GTV-pt (mean increase: 13.3 cm3; range: 0.1–33.1 cm3) and in 17 patients (61%) to a decrease (mean decrease: 4.3 cm3; range: 0.3–9.4 cm3). Sixteen patients (57%) had suspicious lymph nodes as assessed by conventional staging techniques without FDG-PET. Especially regarding lymph node involvement, there was a major difference between observers, both in number as in localization of the nodes (Fig. 5). Delineation of suspicious lymph nodes was not altered by the addition of PET/CT. The PTV increased from 578.0 cm3 (range: 225.2–1015.7; 95% CI: 505.4–650.5) to 581.8 cm3 (range: 279.3–1011.8; 95% CI: 509.87–653.79), which was also not significantly different (P= 0.399).

Table 2. Mean target volumes of three independent observers

Patient number (n=28)	*Mean $GTV_{pt\text{-}CT}$ (cm^3)*	*Mean $GTV_{pt\text{-}PET/CT}$ (cm^3)*	*Mean CTV-CT (cm^3)*	*Mean CTV-PET/CT (cm^3)*	*Mean PTV-CT (cm^3)*	*Mean PTV-PET/CT (cm^3)*
1	8,43	8,10	104,37	101,60	283,63	279,33
2	41,07	39,83	234,47	232,80	517,37	515,17
3	102,37	92,93	493,03	468,00	1015,67	978,03
4	70,43	67,20	352,70	336,47	744,53	700,23
5	33,97	29,80	237,37	224,60	553,83	524,17
6	44,43	49,53	263,37	262,17	582,67	572,60
7	36,70	31,83	279,13	265,80	680,63	658,47
8	22,10	21,23	203,10	205,50	467,60	474,47
9	31,07	29,70	180,40	178,30	417,60	413,00
10	21,27	20,50	184,73	174,00	460,17	438,40
11	116,47	137,20	450,30	505,93	905,97	1011,77
12	20,47	21,07	144,67	147,00	356,13	360,57
13	86,43	80,60	341,37	333,20	700,33	695,43
14	33,73	28,80	293,37	287,53	676,53	670,43
15	57,17	53,23	277,57	255,90	601,03	559,03
16	67,70	59,27	366,00	334,83	790,80	727,90
17	31,03	32,70	217,27	220,93	509,43	505,33
18	107,67	138,00	405,87	467,50	844,73	945,67
19	35,67	31,57	205,20	178,90	491,47	452,70
20	4,77	37,90	79,93	204,37	225,17	457,13
21	36,47	46,63	248,43	268,60	566,43	589,27
22	14,67	11,83	123,00	111,70	311,83	287,00
23	26,93	59,40	216,20	278,53	529,37	609,87
24	54,10	58,30	292,93	301,90	611,17	646,60
25	31,13	42,97	219,80	254,33	491,77	555,07
26	28,93	23,17	190,40	172,50	465,47	436,57
27	92,43	83,60	381,43	358,30	785,23	736,93
28	35,50	30,03	267,53	202,80	596,27	490,17
Mean	**46,18**	**48,82**	**259,07**	**261,93**	**577,96**	**581,83**
95%	**34.4-58.0**	**36.1-61.6**	**220.0-298.1**	**222.6-301.2**	**505.4-650.5**	**509.9-653.8**

CT, computed tomography; CTV, clinical target volume; GTV-pt, gross target volume of the primary tumor; PET/CT, fusion of positron emission tomography and computed tomography; PTV, planned target volume; 95%, 95% confidence interval.

Figure 5. Gross tumor volume of affected lymph nodes



Large differences in number and size of suspicious nodes were seen between different observers. Observer A (pink): 5 small and medium-sized nodes and one large conglomerate, observer B (blue): one medium-sized node, observer C (yellow): three small to medium-sized nodes. Leftside: transmission scan with involved nodes; rightside: coronal cross-section through the largest node.

Geographic misses

In 17 out of 28 patients (61%), addition of FDG-PET to the planning-CT led to cranial and/or caudal adjustment of the original tumor demarcation on the planning-CT; in three patients, both borders of the primary tumor on PET/CT were outside the CT-based CTV; in three patients, the cranial border was above the CT delineation; and in 11 patients, the caudal border was beneath the original delineation. Mean difference in cranial direction was 1.0 cm (range: 0.3–3.0) and in caudal direction 1.1 cm (range: 0.1–5.4). On average, 11% of the volume (three-dimensionally) of the PET/CT-avid CTV was located outside the planning-CT based CTV (range 1–72%, 95% CI: 5–17%).

Concordance indexes

Mean inter-observer CCIs are listed in Table 3. The mean inter-observer CCI among observer pairs in CT-CTVs varied from 55 to 86% (mean: 72%; 95% CI:

69–75%) vs. 47 to 83% in PET/CT-avid CTVs (mean: 72%; 95% CI: 68–75%). Mean concordance indexes in CT- PTVs varied from 61 to 88% (mean: 77%; 95% CI: 74–79%) vs. 54 to 87% in PET/CT-avid PTVs (mean: 76%; 95% CI: 73–80%). These differences were not statistically significant (P= 0.891 and 0.802, respectively).

Table 3. Mean concordance indexes in percentages

Patient number (n=28)	*Mean CCI GTVpt-CT (%)*	*Mean CCI GTVpt-PET/CT (%)*	*Mean CCI CTV-CT (%)*	*Mean CCI CTV-PET/CT (%)*	*Mean CCI PTV-CT (%)*	*Mean CCI PTV-PET/CT (%)*
1	40	46	62	67	69	74
2	81	79	82	82	86	86
3	63	66	68	70	73	76
4	63	77	74	77	79	80
5	64	75	68	75	77	77
6	57	64	72	76	76	81
7	53	52	67	62	73	72
8	68	62	82	82	86	85
9	76	71	72	71	79	79
10	56	76	63	71	67	74
11	68	71	74	74	76	77
12	56	53	70	67	75	72
13	83	82	82	79	86	82
14	75	69	68	64	76	72
15	70	76	76	80	79	83
16	72	66	72	66	79	72
17	73	68	81	78	87	85
18	48	79	55	70	61	73
19	82	74	86	83	88	87
20	48	58	65	69	74	75
21	52	52	73	62	76	68
22	70	69	78	82	82	86
23	66	34	69	47	71	54

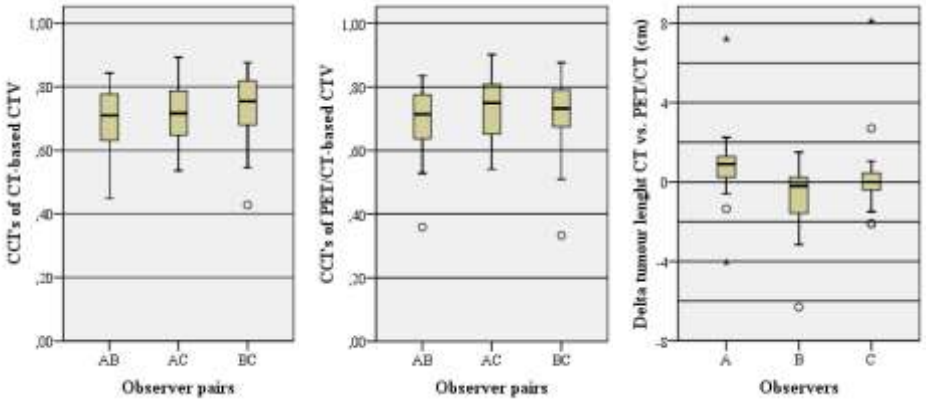
24	67	72	69	67	75	72
25	31	59	57	75	65	80
26	65	53	77	76	79	82
27	86	81	79	75	84	78
28	62	53	63	55	71	59
Mean	**64**	**66**	**72**	**72**	**77**	**76**
95%	**59-69**	**61-70**	**69-75**	**68-75**	**74-79**	**73-79**

Mean concordance indexes in percentages (%). CCI= concordance index, GTVpt= gross target volume of the primary tumour, CTV= clinical target volume, PTV= planned target volume. CT= computed tomography, PET/CT= fusion of positron emission tomography and computed tomography, 95%=95% confidence interval.

Observer dependent differences

Grouped by each observer pair, there were modest differences between CCIs of different pairs, both for CT as PET/CT delineation (Fig. 6). These differences were not statistically significant. The mean difference in tumor length, grouped by observer, was nearly zero after application of PET/CT imaging, and therefore, was not observer-dependent.

Figure 6. Box plots of concordance indexes between observer pairs for CT-based CTV and PET/CT-based CTV (on top) and delta tumor lengths for each observer (below)



CCI, concordance indexes between observer pairs, delta tumor length, tumor length on CT minus tumor length on PET/CT. Differences between observers are visible, as observer B altered his delineation much more than A and C.

Discussion

Radiation oncologists determine the various radiation volumes on all clinical and radiographic examinations as all results are complementary to each other with different contributions to give. Although logical, the additional value of FDG-PET to current CT-based radiotherapy planning still is unclear.

The main purpose for successful irradiation is delivery of an optimal radiation dose on tumor tissue with a minimum of geographic misses on the one side and a minimum of irradiation injury of healthy tissue on the other side. However, a major clinical issue still remains unresolved; target volume delineation itself remains uncertain as it is prone to a large inter-observer variability.13,14 In this study, we showed that incorporation of FDG-PET in CT-based radiation planning for esophageal tumors may be important, as software-based PET/CT had major effects on target volume definition in 61% of the subjects (17/28) with a rate of 11% of the volume of the PET/CT based CTVs situated outside the CT-based target volumes. In this way, PET/CT has the potential to avoid geographical misses. With concordance indexes of 63–76% for different target volumes, observer variation remains one major determinant of target delineations. We observed neither significant improvement nor deterioration by PET/CT on the inter-observer variability.

Incorporation of FDG-PET in radiotherapy planning has been mainly investigated in non-small-cell lung cancer and head and neck cancer and an increasing number of studies in esophageal cancer demonstrate its significant impact on target definition as well.15,16 Recently, Hong et al. compared two different PET/CT-based techniques with CT-only based esophageal tumor definition. Both manual and semiautomatic contouring on specific thresholds affected target definition, though the two PET/CT-based techniques produced significantly different tumor volumes in 15 patients (56%).17 Another study reported a substantial reduction of target volumes by using PET/CT in treatment planning in a large majority of patients (63% of esophageal patients

vs. 86% of lung cancer patients).18 Konski et al. also found a significant smaller tumor length of 5.4 cm (95% CI: 4.4–6.1 cm) on PET/CT compared with 6.8 cm on CT (95% CI: 5.6–7.9 cm).19 Leong et al. reported that the CT-based GTV excluded PET-avid disease in 11/21 patients (69%), and a geographic miss of gross tumor in 5/21 patients (31%). The discordance between CT and PET/CT was due mainly to differences in defining the longitudinal extent of disease in the esophagus.4 In the study of Moureau-Zabotto et al., PET/CT fusion appeared to decrease the GTV in 12 (37%) of the 43 patients, owing to a reduction in tumor length. However, PET/CT fusion also appeared to increase the GTV in 21% (n= 7), owing to an increased tumor and the detection of occult lymph node metastases.20

Spatial resolution of an FDG-PET is limited to at least 5 mm. Therefore, small suspicious lymph nodes may be missed on FDG-PET. Difficult decisions may occur when there is no consensus regarding lymph node metastases between FDG-PET and CT/EUS. Not including suspicious lymph nodes on CT or EUS in the target volume based on negative FDG-PET imaging would be incorrect and may have serious consequences. However, the radiobiological significance of FDG-negative tumor margins remains unclear until the longer-term outcomes data come through to show that FDG-based definition of treatment volumes really does improve the therapeutic index. Conversely, including false positive nodes in the target volume may lead to an increased radiation field with the possibility of late radiation toxicity.

In this study, we chose for tumor delineation the method which is described as superior by Nestle et al. using the mean activity of the liver as reference value for physiological soft tissue uptake of FDG under fasting conditions. Other semi-quantitative methods used for tumor contour definition by FDG-PET are visually correlation, the use of an FDG intensity level with a threshold of 40% of the maximum SUV, and the use of an isocontour of SUV = 2.5 around the tumor.21 Of these three different techniques, a cut-off value of 2.5 SUV

provided the closest estimation in radiotherapy planning. Since other studies measured substantially different volumes with these techniques, especially in inhomogeneous tumors, they appeared to be less accurate and less reproducible than the method which uses liver FDG-uptake as cut-off value.12,22

In software fusion, time and patient positions are different for CT and PET scanning. Because difference in patient positions, i.e., arms above the head for CT and arms beside the body for PET and respiratory activity between the CT plan and PET/CT, it is difficult to compare tumor volumes and lengths, particularly when the differences are small. CT imaging is usually performed in maximum inspiration in several seconds and FDG-PET imaging is completed in half an hour of moderate respiration. In the last few years, hybrid PET/CT scanners together with respiration-gated acquisition are more and more used for staging properties, but not yet in radiotherapy planning. This study indicates what could be the impact of hybrid PET/CT on target volume planning and inter-observer variability. Further investigations, including pathological examination on resected specimen are needed for a standard use of hybrid PET/CT in the radiation planning of esophageal tumors.

In conclusion, incorporation of FDG-PET imaging in CT-assisted volume definition seems to have a great impact on target volume definition with the potential to reduce geographical misses, though without significant interference of the inter-observer variability.

Acknowledgment

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Chapter 5

Consequences of additional use of PET information for target volume delineation and radiotherapy dose distribution for esophageal cancer

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Abstract

Background and Purpose

To determine the consequences of target volume (TV) modifications, based on the additional use of PET information, on radiation planning, assuming PET/CT-imaging represents the true extent of the tumour.

Materials and Methods

For 21 patients with esophageal cancer, two separate TV's were retrospectively defined based on CT (CT-TV) and co-registered PET/CT images (PET/CT-TV). Two 3D-CRT plans (prescribed dose 50.4 Gy) were constructed to cover the corresponding TV's. Subsequently, these plans were compared for target coverage, normal tissue dose–volume histograms and the corresponding normal tissue complication probability (NTCP) values.

Results

The addition of PET led to the modification of CT-TV with at least 10% in 12 of 21 patients (57%) (reduction in 9, enlargement in 3). PET/CT-TV was inadequately covered by the CT-based treatment plan in 8 patients (36%). Treatment plan modifications resulted in significant changes ($p < 0.05$) in dose distributions to heart and lungs. Corresponding changes in NTCP values ranged from −3% to +2% for radiation pneumonitis and from −0.2% to +1.2% for cardiac mortality.

Conclusions

This study demonstrated that TV's based on CT might exclude PET-avid disease. Consequences are under dosing and thereby possibly ineffective treatment. Moreover, the addition of PET in radiation planning might result in clinical important changes in NTCP.

Introduction

Esophageal cancer is an increasing health problem in the Western world. In the Netherlands, the incidence has doubled in the last twenty years.[1,2] In the last decades, surgery has been the primary treatment modality for esophageal cancer. However, combined chemoradiotherapy is increasingly applied, either as definitive therapy or in the neoadjuvant setting prior to a curatively intended surgical .[3]

With modern radiation delivery techniques, accurate delineation and subsequent adequate irradiation of the tumour volume is a prerequisite for successful treatment. However, tumour definition is often hampered by the poor discriminative value of the currently used imaging modalities, in particular computed tomography (CT) and the inability to relate endoscopic (ultrasound) information to CT images. The addition of positron emission tomography (PET) information may improve accuracy in the delineation process. 18F-Fluoro-2-deoxy-d-glucose (FDG) PET provides additional information on the metabolic activity i.c. glucose utilization of the tumour. Because FDG-PET adds functional information to the anatomical information of CT, tumour visualisation and thus tumour delineation may improve.

Another problem in radiotherapy (RT) is the co-irradiation of normal tissues, while irradiating the tumour. Thoracic irradiation may result in heart, lung and esophageal injury and subsequent late radiation-induced side effects.[4-6] The clinical relevance of these side effects is increasing when survival rates improve. In the last decades, the overall survival of patients with esophageal cancer, who received radiotherapy with curative intent, has improved, especially when radiotherapy is combined with concurrent chemotherapy.[7,3,8] However, the probability of treatment-related side effects has increased as well.[9,10] Therefore, the reduction of normal tissue co-irradiation and the subsequent normal tissue complication probabilities (NTCPs) has become increasingly important.

Numerous investigators have shown that the addition of PET, or integrated PET/CT, into the radiotherapy planning process results in target volume modifications.[11-16] These modifications will result in adjustments of radiation treatment plans, which might also effect co-irradiation of normal tissues.[13]

The purpose of the present study was to determine the changes in tumour delineation and subsequent target volumes due to the additional use of PET information, compared to the use of CT alone. Secondly, we investigated the possible consequences of target volume modifications with regard to co-irradiation of the normal tissues and the subsequent changes in NTCP values based on validated NTCP models.

Methods and Materials

Patients

The study population was composed of 21 consecutive patients who met the following eligibility criteria: histological confirmed esophageal cancer (adeno- or squamous cell carcinoma); stage T2-4, N0-1, M0-1a; without recent thoracic surgery and/or stenting.

All patients were staged according to the TNM-system of the Union International Contre le Cancer (UICC) [17], based on the following examinations: physical examination, endoscopic ultrasonography (EUS), cervical/thoracic/abdominal CT, whole body FDG-PET. Fine needle aspiration biopsy or other additional investigations were carried out when indicated.

All patients provided informed consent. The 21 patients had a mean age of 63 years (range: 48–76 years). Patients and tumour characteristics are listed out in Table 1

Imaging

Radiotherapy treatment planning was determined using CT and FDG-PET images, made within 2 weeks after the initial diagnosis.

A 16 or 64 multidetector row spiral CT scanner was used (Somatom Sensation, Siemens Medical Systems, Erlangen, Germany). After administration of intravenous contrast agents, 3 mm CT images were obtained in cranial–caudal direction, including tumour, lymph node areas, lungs and liver. Lymph nodes with a diameter of 10 mm or more were considered to be pathological, as well as round, hypo dense lymph nodes measuring >5 mm.

The FDG-PET-scans were performed with an ECAT 951/31 or an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA). The 951/31 acquires 31 planes over 10.9 cm, while the HR+ acquires 63 planes over a 15.8 cm axial field of view. Patients had to fasten for at least 4 h before 130–750 MBq FDG (mean 362 MBq, depending on body weight) was administered intravenously. Ninety minutes after intravenous contrast injection, emission scans were performed for

5 min per bed position from the crown to mid-femur. To distinguish tumour from normal tissue we used the method described by Nestle et al.[18] According to this method, FDG-PET images are normalised reference to the physiological

Table 1. Patient characteristics

Characteristics	**N=21 (%)**
Sex	
Male	16 (76)
Female	5 (24)
Age (years)	
Median	63
Range	48–76
Histology	
AC	17 (81)
SC	4 (19)
Localisation	
High	3 (14)
Low	16 (76)
GEJ	2 (10)
Clinical stage	
T2N0M0 3 (14)	3 (14)
T3N0M0 7 (33)	7 (33)
T3N1M0 8 (38)	8 (38)
T4N1M0 1 (5)	1 (5)

Abbreviations: AC, adenocarcinoma; SC, squamous cell carcinoma; GEJ, gastro-esophageal junction. Clinical stage, staging based on clinical examination, endoscopic ultrasound, computed tomography, positron emission tomography, additional investigations when necessary, but without FDG-PET/CT co-registration.

FDG uptake in the liver. FDG uptake was scored on a four-point scale of intensity: 'normal' (physiological), 'slightly increased', 'moderate increased' and 'intensely increased'. All 'moderate increased' and 'intensely increased' lesions

were defined as hotspot. Suspect lesions were verified if possible by fine needle aspiration biopsy (FNAB).

FDG-PET images were co-registered with the CT images on a Siemens Workstation using the Oncentra MasterPlan 1.5 software program (Nucletron, Veenendaal, The Netherlands). An experienced physician carried out the co-registration process.

Tumour delineation

All CT images were reviewed by two experienced radiologists, while the FDG-PET images were reviewed independently by two experienced nuclear physicians.

The tumour volume was defined by an experienced radiation oncologist, using additional information of EUS, FNAB outcome, physical examination and reports of CT and PET (only for PET/CT delineation). The gross tumour volume (GTV) was first delineated on CT images, and second, independent and blinded, to the co-registered PET/CT images. The GTV contained the primary tumour and pathologic lymph nodes. The clinical target volume (CTV) was obtained by adding a 1 cm margin in transversal plane and a 3 cm margin in cranial–caudal direction (2 cm margin if the tumour expanded into the stomach) to the primary tumour and 1 cm margin around pathological lymph nodes. In addition, the CTV was adjusted to anatomical structures such as bones. The planning target volume (PTV) was generated by expanding the CTV with 1 cm margins to account for setup uncertainties.

The primary tumour length was measured in cranial–caudal direction, based on CT and PET/CT co-registration. Volumetric analysis of the GTV's and CTV's was performed to determine the proportion of PET-positive disease that was excluded if CT information alone was used for tumour definition. The CT-based and PET/CT-based volumes were quantitatively compared by means of an index of conformality, as described by Gondi et al.[12] This index represents the ratio of

the intersection of two volumes of interest to their union, i.e., the percentage of the total volume that overlaps. A value of 1 implies that the volumes are equal, while a value of 0 indicates that there is no overlap between the two volumes.

We used the same principle to calculate the percentage of PET/CT-GTV located outside the CT-GTV. The Geographic Miss Index (GMI) was estimated by dividing PET/CT-GTV minus the intersection, by the PET/CT-GTV in total. In this case, a value of 0 indicates that the PET/CT-based GTV is covered totally by the CT-based GTV, while a value near 1 implies that the PET/CT-GTV is completely different from the CT-GTV. Similarly, we quantified the proportion of PET/CT-GTV excluded by the CT-CTV. This type of geographic mismatch might result in inadequate dose coverage of the primary tumour, assumed that PET/CT represents disease extension best. PET-avid disease incorporated by the CT-based CTV seemed more relevant than inclusion by the CT-PTV; in this study, set up uncertainties are irrelevant, since they are identical (same patient).

Organs at risk, such as lungs, heart, liver and spinal cord, were outlined on CT images. The heart was contoured to the level of the pulmonary trunk superiorly, including the pericardium, excluding the major vessels. Lungs were considered as one organ.

Radiotherapy planning

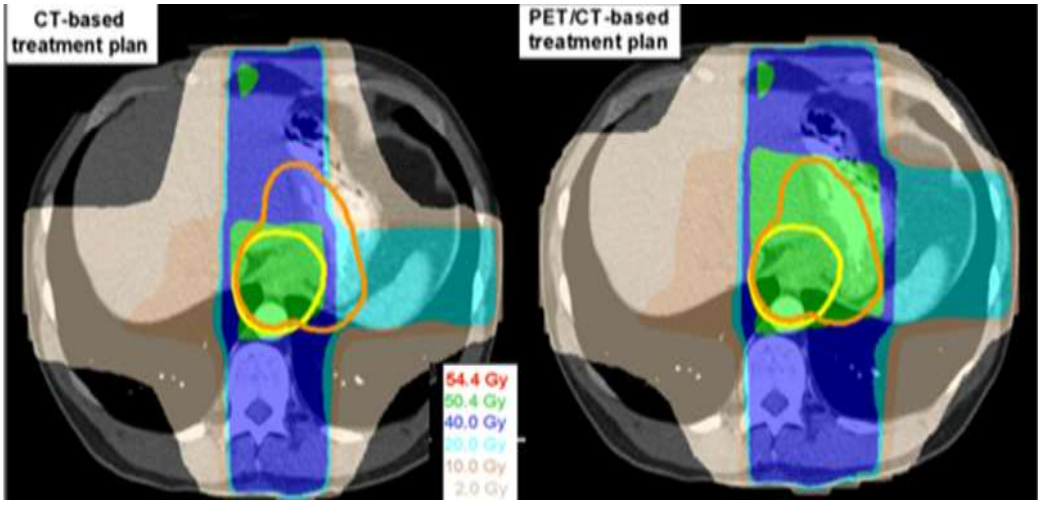
3D-conformal RT (3D-CRT) plans were made, using 1.8 Gy per fraction to a total dose of 50.4 Gy. A commercial treatment planning system (Pinnacle TPS version 8.0d, Philips Radiation Oncology Systems, Milpitas, CA) was used to design a RT plan that would cover 98% of the PTV with at least 95% of the prescribed dose. A 3-field technique (anterior, posterior and left lateral) was applied in all patients using two small additional manually shaped beams, if necessary. The iso-centre and dose-specification point were placed centrally in the PTV. Wedges and MLC shielding were applied to fit the 95%-isodose closely around the PTV

in three dimensions, and to obtain a uniform dose distribution according to the recommendations of the International Commission on Radiation Units and Measurements (ICRU).[19]

If possible without reducing the target coverage, the following dose constraints were maintained; spinal cord < 50 Gy; mean lung dose (MLD) < 20 Gy, lung V20 < 30%, heart V40 < 30% and liver V30 < 60%.

First, RT planning was based on CT-based target volume definition (CT-PTV). Second, the plans were modified to cover PET/CT-PTV (Fig. 1). In case planning optimisation was not compromised, factors as wedge fractions, beam weighting and the dose- normalisation point were kept constant.

Figure 1. Dose coverage in PET/CT- and CT-based treatment plans



Yellow, CT-based PTV, orange, PET/CT-based PTV. The CT-based plan covers the CT-PTV contour, but shows under dosing of the PET/CT-PTV. The PET/CT-based plan covers the PET/CT-PTV, while the CT-PTV is incorporated by the PET/CT-radiation field as well.

Treatment planning evaluation

To assess the implications of normal tissue irradiation, treatment planning software (Pinnacle TPS version 8.0d, Philips Radiation Oncology Systems, Milpitas, CA) was used to obtain several dosimetric values from the dose–volume histograms (DVHs), including the mean heart dose, proportion of heart

receiving 40 Gy (V40), mean lung dose, spared lung volume (receiving 5 Gy) and relative volume of lung receiving 20 Gy (V20).

Target coverage was determined by evaluating proportions of CT- and PET/CT-based PTV receiving at least 95% of the prescribed dose. Coverage was considered inadequate if less than 96% of the target volume received 95% of the prescribed dose. This threshold was set at 96% instead of 98% to discard small neglectable differences between the treatment plans. Validated NTCP models were used to evaluate the potential clinical relevance of changes of NTCP values for the comparison of CT- and PET/CT-based treatment plans.

The NTCP for symptomatic radiation pneumonitis, lungs considered as one organ, was calculated with model parameters (TD50 = 29.9 Gy, m = 0.41, n = 1, α/β = 3 Gy) derived from the meta-analysis published by Semenenko and Li.[20] This model was based on cumulative experience at various institutions. The NTCP for cardiac mortality after 10–15 years was calculated based on a seriality model derived by Gagliardi et al.[6] Therefore the following parameter values were used; D50 = 52.3 Gy, γ = 1.28, s = 1, α/β = 3 Gy.

Both models consider three parameters; the dose giving 50% complication probability (TD50), volume dependence (n/s) and the steepness value of the dose–response curve (m/γ). Influence of altered fractionation dose was taken into account, with a reference dose of 2 Gy.

Statistical analysis

For comparison of the CT- and PET/CT-based plans, various dosimetric parameters were analysed using SPSS 16.0 software. The Wilcoxon signed rank test was used to determine the statistical significance of the differences between these parameters. Tumour lengths were compared the same way. P-values <0.05 were considered statistically significant.

To give insight in the real differences between the two treatment plans, we divided the ones showing an increase from the ones showing a reduction in order to avoid mediation of the differences.

Results

Tumour delineation

The addition of PET resulted in a change in average tumour length of 73 mm (range: 32–140 mm) on CT to 65 mm (range: 23–135 mm) on co-registered PET/CT ($p = 0.02$).

The addition of PET reduced the tumour length in 11 of 21 patients (52%) with a mean reduction of 17 mm (SD: ±13 mm), while increased tumour length was seen in 5 patients (24%) with a mean increase of 6 mm (SD: ±4 mm). To avoid a partial volume effect, differences smaller than 3 mm (slide thickness) were considered equal. This was the case in 5 other patients (24%). Adjustment of the GTV with more than 10% was seen in 62% of the cases; 9 patients (43%) showed a GTV reduction, while in 4 patients (19%) the addition of PET resulted in an enlargement of the GTV.

Adjustments regarding GTV were mainly seen at the caudal/cranial extent of the tumour. Therefore, we did not analyse the volumes separately. Volume modifications correlated with length modifications and were considered in the volume indexes.

The mean GTV Conformality Index (CI) was 0.68 (range: 0.01–0.94; SD ±0.22); 68% of the PET/CT- and CT-GTV's overlapped. The CTV- and PTV-CI's were 0.78 (range: 0.22–0.97; SD ±0.16) and 0.81 (range: 0.31–0.96; SD ±0.14), respectively.

Assuming that PET/CT represents the true extent of the tumour, exclusion of PET/CT-based disease by CT-based target volumes would be more interesting than the conformality of CT- and PET/CT-based volumes. Therefore the GTV Geographic Miss Index (GMI) was calculated. The average GTV-GMI was 0.16; 16% (range: 0–99%; SD ±0.24) of the PET-avid disease was located outside the CT-GTV. In 13 patients (61%) more than 5% of the PET/CT-GTV was excluded by the CT-based GTV. The mean CTV and PTV GMI were 0.10 (range: 0.01–0.76; SD ± 0.14) and 0.08 (range: 0.01–0.65; SD ±0.17).

To determine the possible inadequate dose coverage of the PET-based tumour volume, PET/CT-GTV and CT-CTV (counting for microscopic tumour spread) were compared, showing in one patient a PET-tumour volume exclusion of 60%.

Treatment planning evaluation: dose coverage by CT-based plans

For all patients, 98.0–98.5% of the CT-PTV received 95% of the prescribed dose. The PTV's based on PET/CT were, however, inadequately covered by the CT-based treatment plan in 8 of 21 patients (38%). The median coverage, receiving 95% of the prescribed dose, was 92%. In three cases (14%) the coverage was below 90%, of which one was even below 42%, demonstrating the importance of accurate tumour delineation. Geographic mismatches can result in inadequate coverage's, resulting in under dosing (Fig. 1) of the tumour and thereby possibly ineffective treatment.

The PET/CT-based GTV was inadequately covered by the CT-based plan in one patient, with 80% coverage.

Treatment planning evaluation: normal tissue radiation exposure

Dose coverage of the corresponding PTV's maintained between 98.0% and 98.5%, for both CT- and PET/CT-based treatment plans. The radiation dose did not exceed the normal tissue tolerance doses, except for the heart V40 in 6 patients, where PTV overlapped with the heart.

DVH analysis was performed to determine the consequences of tumour volume modifications for normal tissues. An overview of the normal tissues radiation exposure, comparing CT- and PET/CT-based plans, is shown in Table 2.

Table 2. Mean dose delivered to normal tissues; differences between CT- and PET/CT-based treatment plans

Normal tissue	*N*	*CT-based plan (Gy ± SD)*	*PET/CT-based plan (Gy ± SD)*	*Difference (absolute) (Gy ± SD)*	p-Value[a]
Normal tissue radiation exposure					
Lung					
V20-all (%)	21	19.4 (±5.7)	18.2 (±4.7)	-1.2	0.06
V20-increase (%)	6	15.3 (±5.6)	17.1 (±6.0)	1.8	0.03
V20-decrease (%)	11	21.9 (±5.0)	18.7 (±4.4)	-3.2	0.00
MLD-all (Gy)	21	10.8 (±2.7)	10.3 (±2.3)	-0.3	0.08
MLD-increase (Gy)	6	9.0 (±2.9)	9.7 (±3.1)	0.7	0.03
MLD-decrease (Gy)	11	11.9 (±2.2)	10.5 (±2.0)	-1.4	0.00
Heart					
V40-all	21	28.4 (±11.1)	26.3 (±10.8)	-2.1	0.07
V40-increase (%)	5	24.5 (±11.1)	27.3 (±11.9)	2.8	0.04
V40-decrease (%)	13	32.3 (±10.5)	27.9 (±11.1)	-4.4	0.00
Liver					
V30 (%)	21	9.3 (±5.6)	8.3 (±5.9)	-1.0	0.10
Spinal cord				-0.5	
D_{max} (Gy)	21	44.6 (±4.0)	44.1 (±3.6)		0.78

Abbreviations: V20, percentage of total lung volume receiving >20 Gy; MLD, mean lung dose; V40, percentage of total heart volume receiving >40 Gy; V30, percentage of total liver volume receiving >30 Gy. Dmax, maximum dose delivered to spinal cord. [a] Wilcoxon signed rank test.

On average, the incorporation of PET information in the radiation planning did not result in statistically significant differences in any of the dosimetric factors analysed. However, significant differences in heart and lung radiation exposure between the CT- and PET/CT-based treatment plans were revealed when we separated the cases with increased values from the ones with decreased values. Differences were largest for V40 heart, showing a mean decrease of 4.4% and a mean increase of 1.7%.

Modifications in normal tissue dose distribution resulted in the corresponding NTCP changes (Table 3). The absolute difference in NTCP value for symptomatic radiation pneumonitis ranged from +2% to −2.7%. Eleven of 21 cases (52%) showed a mean reduction of the NTCP value of 1.4% (SD: ±0.8). An increase in NTCP was seen in 6 patients (29%), with a mean value of 0.7% (SD: ±0.7). Individually, the differences can be of great importance as is demonstrated in Fig. 2. Moreover, the relative differences were large and ranged from +34.3% to 28.9%. For the risk of cardiac mortality, modifications in normal tissue dose distributions resulted in a mean NTCP reduction of 0.5% in 13 patients (62%) (range: 0.11–1.20). The NTCP value increased in 6 patients (range: 0.05–0.23), with a mean value of 0.1%.

Discussion

In this study, the addition of PET revealed possible geographic misses when the radiotherapy planning was based on CT alone. PET-avid disease (GTV) was excluded by the CT-based GTV with more than 5% in 13 patients (61%). Geographic mismatches can result in inadequate coverage's, resulting in under dosing of the tumour and thereby possibly ineffective treatment. In this study, PET/CT-based target volumes (PTVs) were inadequately covered by CT-based radiation plans in 8 patients (38%).

In the current study, the term 'geographic misses' was based on the assumption that PET/CT represents the true extent of the tumour. However, the question arises whether this is justified as data from well-designed studies on this subject are very limited. One study reported an incremental effect of PET on the accuracy of initial staging over CT of 14%.[21] Others reported a significant positive correlation between PET-based tumour length, estimated for different SUV thresholds, and pathologic findings.[22,15] Mamede et al. also found a correlation between PET-based tumour length and the tumour length based on EUS, the gold standard for T staging.[22] Konski et al. also demonstrated that EUS measurements of tumour length closely approximated PET tumour measurements.[14] In that study, they used a SUV threshold for malignancy of 2.5. These results indicate that PET-based GTV definition is more accurate than CT-based GTV definition.

Leong et al. also evaluated the impact of FDG-PET on CT-based radiotherapy treatment planning.[11] They found an exclusion of PET-avid disease in 11 patients (69%), with a median exclusion of PET/CT-GTV of 38%. Discordances between PET/CT- and CT-based GTV resulted in an inadequate coverage of the PET/CT-PTV by the CT-plan in 38% (6/16) of the patients. Similar results were found in the current study.

Internal mobility of the tumour due to breathing movements can cause differences in tumour localisation if images are acquired at different times during the respiratory cycle. PET is performed over many respiratory cycles, while in the current study CT imaging was performed in several seconds, capturing part of the respiratory cycle. However, these differences are expected to be rather small and will be mainly seen in the distal esophagus.[23] To avoid these differences in tumour localisation, 4D-PET/CT-imaging should be used to synchronise the respiratory cycle.

The addition of PET information may either result in a reduction of tumour volume or an enlargement. Several other studies described similar modifications.[11-16] Vrieze et al. claimed however, that GTV should not be reduced based on negative PET findings, because of the low sensitivity of FDG-PET in esophageal cancer.[16] Enlargement of the GTV was justified, based on the high specificity of PET. However, Vrieze et al. focused on the detection of pathologic lymph nodes regions, instead of tumour extent.

PET had trouble to distinguish adjacent lymph nodes from primary tumours with high FDG-accumulation. CT can make characterization of the FDG-activity easier by providing an anatomical context. Sensitivity for diagnosing lymph node metastases improved significantly by using PET/CT, compared to PET alone.[24,25,21] CT, on the other hand, has limited ability detecting normal-sized pathologic lymph nodes. In these cases, the addition of the functional information of PET can improve the sensitivity. However, tumour involved lymph nodes <5 mm are difficult to detect by PET.[26] Combined PET/CT resolves most of the individual shortcomings of PET and CT, and showed to be more sensitive in the diagnostic process than these images modalities individually. Therefore it is not right to claim that the addition of PET should not lead to a reduction of the GTV's of lymph nodes, based on the limited sensitivity of PET alone compared to CT alone.

Usable SUV thresholds, based on a certain SUV-level or a percentage of the maximal SUV, to distinguish pathologic from normal tissue, could not be determined for esophageal cancer.[15,27] SUV measurements are influenced by many factors, such as patient preparation procedures, scan acquisition, image reconstruction and data analysis settings, which make them less accurate and less reproducible. Therefore, visual interpretation was used for target volume delineation in the current study.

Assuming that PET/CT represents the true extent of the tumour, tumour definition based on CT can result in geographic misses, with consequently under dosing of the tumour and thereby possibly ineffective treatment. Button et al. described sites of first recurrences of esophageal cancer after irradiation with EUS and CT-based treatment plans.[28] The relapses were mainly seen within the radiation field (within PTV); 65% of the relapses were local recurrences. Only 3 patients (4%) developed regional recurrences outside the radiation field. These results suggest that the target volumes were adequately defined in the fast majority of cases. Only 3 cases could be considered possibly preventable by the additional use of PET. However, localisation of the relapses was considered in relation to the PTV (within or without the PTV), accounting for patient set up variations. Because of these variations, the real irradiation dose in the PTV is always lower. Therefore, in order to get a more accurate picture on the real percentage of the possibly preventable recurrences, the number of recurrences outside the CTV rather than outside the PTV is most relevant.

The addition of FDG-PET will probably not improve the delineation of T1-tumours; PET has trouble detecting these tumours, especially of T1a (remaining within the muscularis mucosae).[21,26] As no gain was expected for T1-tumours, they were excluded from this study.

GTV modifications by the use of PET/CT, resulted in adjusted CTV's and PTV's and the subsequent radiation treatment plans, resulting in changes in dose distributions to heart and lungs. We found significant reductions of V20 lung,

MLD and V40 heart when PET was added to CT. In individual cases, these reductions can be of clinical relevance, as illustrated by the NTCP models of Semenenko and Li and Gagliardi et al.[20,29] However, the impact in terms of changes in NTCP values, resulting of dose–volume modifications, depends on the range in which these changes occur and the corresponding steepness of the NTCP curve. In this cohort, we found a MLD reduction in the 7–14 Gy dose range, resulting in a NTCP reduction within a range of 1–3%. In case of dose escalation to 60 Gy (radiotherapy only) the impact on the estimated NTCP values will be much larger, because the MLD changes are seen in a higher dose range, corresponding to the increased prescribed dose.

Chemotherapy seems also associated with the incidence of radiation pneumonitis. Studies comparing radiotherapy with concurrent chemoradiotherapy suggest that chemotherapy can be a risk factor for grade 2 pneumonitis.[10,9] This implies that minimization of radiation dose to the organs at risk, would be even more beneficial when concurrent chemotherapy is given.

NTCP models have their shortcomings, as well as the models used in the current study. The NTCP model by Semenenko is based on lung cancer patients. Although these patient groups seem comparable, because of their intra thoracic tumours, other factors such as co-morbidity are probably different in these groups, which might affect the NTCP as well. For cardiac mortality, we used the model of Gagliardi, in the absence of a NTCP model based on patients with esophageal cancer. Gagliardi based his NTCP model on data sets of breast cancer patients, who were irradiated. However, the irradiation technique for beast cancer differs from the one used for esophageal cancer. Subsequently, the dose distribution to the heart will be different, which might have consequences for the NTCP values. Since it remains to be clarified which parts of the heart are involved in developing cardiac toxicity, the estimated NTCP values in this paper should be interpreted with great caution.

For more accurate estimation of the NTCP, more research regarding side effects after the irradiation of esophageal tumours is required. Enlargement of the GTV (based on PET/CT) will increase co-irradiation of normal tissues and therefore the estimated complication risks. In our study, enlargement of the target volume and consequently the changes in NTCP were limited. However, if we enlarge the target volumes according to Vrieze et al., the changes in normal tissue dose distribution will be much larger. In clinical practice, this method is probably seen more often, based on the uncertainty of the radiation oncologist. However, PET/CT seems to improve the confidence of the oncologist regarding their contours.[30]

In case of GTV enlargement, it would be relevant to determine whether possible benefits of more (accurate) irradiation outweigh to the increased complication risks. Effects of GTV enlargement on locoregional control and survival are however unknown. More research regarding treatment outcome and possible side-effects/complication risks needs to be done.

Conclusions

This study demonstrated that tumour volumes based on CT might exclude PET-disease, resulting in a geographic miss. Consequences for treatment plans are under dosing and thereby possibly ineffective treatment. Moreover, the results showed that the addition of PET led to changes in dose distributions to normal tissues, which might be of clinical importance in individual cases. To determine whether the changes based on the addition of PET to CT will result in higher probabilities on local control, prospective studies are needed in which recurrence analysis, i.e., relating local recurrence position to dose distributions, are investigated

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Part IV

FDG-PET and Prognostic Biomarkers

Chapter 6

Prognostic impact of clinicopathological features and the expression of biomarkers related to 18F-FDG uptake in esophageal cancer

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Abstract

Purpose

To analyze the prognostic impact of tumor biomarkers related to 18-F-fluoro-deoxyglucose (FDG) uptake and clinicopathological factors in esophageal cancer.

Materials and Methods

Maximum standardized uptake values (SUV_{max}) measured on preoperative FDG-positron emission tomography (FDG-PET) scans were compared with tumor characteristics in 47 consecutive patients after a curative esophageal resection without preoperative chemoradiotherapy. Expression levels of hexokinase-II (HK-II), glucose transporter I (GLUT-I), hypoxia inducible factor-1α (HIF-Iα), vascular endothelial growth factor-C (VEGF-C), p53, and proliferative activity (MIB-I score) were correlated with clinicopathological characteristics, SUV_{max} and survival data.

Results

High HK-II expression was correlated with reduced SUV_{max} values (p= 0.002) and significantly higher among adenocarcinoma (p = 0.005). Pre-operative high FDG uptake in primary tumors was associated with nodal metastases (pN1; Spearman correlation 0.39, p= 0.01). A pre-operative SUV_{max} of > 3.67 predicted significantly lower disease free survival (DFS) and distant recurrence free survival (p= 0.022 and p =0.005). The 5-year estimated overall survival (OS) in patients with >4 lymph node metastases (LNM >4; n=15) was 0% and 30% in low vs. high GLUT-I/p53 expressing tumors, respectively (p=0.018). In patients with lymph node positive (N+) and/or advanced (T3/T4) tumors, the 5-year estimated OS was 16% in loss of p53/low GLUT-I expression and 40% in high p53/high GLUT-I expression (p=0.025).

Conclusions

Pre-operative FDG-uptake as SUVmax predicts nodal metastases in esophageal cancer. Recurrence rates were significantly higher in tumors with a SUV_{max} of > 3.67. LNM >4 or locally advanced disease combined with loss of p53 and weak GLUT-I expression strongly diminished OS.

Introduction

Cancer of the esophagus has a dismal outcome mainly due to its aggressive biological behavior. Many patients present with distant metastases or locally advanced disease.18-F-fluoro-deoxyglucose positron emission tomography (FDG-PET) or combined computed tomography (PET-CT) has a pivotal role in detecting distant metastases.[1-3] FDG uptake is measured semi-quantitatively as standardized uptake values (SUVs). Many studies demonstrated that the maximum SUV (SUV_{max}) symbolizes tumor aggressiveness and provides additional prognostic information.[4-7] The majority of tumors are characterized by high metabolism rates, enhanced DNA synthesis / cell proliferation, hypoxia, and induction of apoptosis. The enhanced glycolysis in high-grade tumors, due to increased metabolic activity, is known as the Warburg effect. High glucose uptake and metabolic activity are associated with increased expression of glucose transporters (primarily subtype GLUT-I) and an increased phosphorylation of glucose by hexokinase (primarily subtype HK-II).[8,9] Glycolysis and angiogenesis are also increased as a response to hypoxia with expression of hypoxia-inducible factor (HIF-1α).[8,10,11] Several studies reported vascular endothelial growth factor (VEGF) as a prognostic factor in esophageal cancer (EC), because it enhances tumor lymphangiogenesis (VEGF-C).[12-15] Poor overall survival and tumor cell growth are significantly correlated, characterized by a high cellular proliferative index (KI-67 index), represented by the monoclonal antibody MIB-I.[16] P53 gene mutations are also involved in early carcinogenesis.[17,18] Wild type p53 causes cycle arrest in response to DNA damage and is of great importance in the apoptosis regulation.

Aim of this study was to determine the association between SUV_{max} and the expression patterns of HK-II, GLUT-I, HIF-Iα, VEGF, p53 and MIB-I versus the prognosis of EC patients after curative resection.

Material and Methods

Patients and clinicopathological features

Forty-seven patients (38 males and 9 females) after curative (R0) transthoracic oesophagectomy were consecutively enrolled between 2002 and 2004. Patient and tumor characteristics are given in table 1. The mean age was 64 years and the mean tumor length was 5.5 cm. Informed consent was obtained from all patients with approval of the institutional board. In this retrospective study we included solely patients without preoperative chemoradiotherapy, conform the standard treatment until 2005. FDG-PET was performed within two weeks before oesophagectomy. Staging also contained endoscopic ultrasonography (EUS) and 64-detector computed tomography (CT). Tumor length was calculated during EUS. After surgery, the resected specimens were embedded in paraffin and sections were immunostained with antibodies glucose transporters (GLUT-I, HK-II), apoptotic/proliferation markers (p53, MIB-I), VEGF-C, and HIF-Iα.

FDG-PET protocol and image analysis

Whole body FDG-PET was performed with an ECAT HR+ positron camera (Siemens/CTI, Knoxville, TN, USA). The HR+ acquires 63 planes over a 15.8 cm axial field of view. Patients were fasted for 4 hours before FDG was administered intravenously. The mean administered activity was 324 ± 87 MBq (range, 130-530). Data acquisition started in whole body mode 90 minutes after injection, for 5 minutes per bed position from the crown to the mid femur. FDG-PET images were generated on basis of attenuation-corrected transaxial images, amount of FDG in MBq, body weight, and cross calibration factors for PET and a dose calibrator. All images were reviewed by a dedicated nuclear physician and radiologist. FDG-uptake in the primary tumor was quantified in SUV. The maximal SUV (SUV_{max}) was calculated from the concentration of radioactivity in the tumor by the formula: MBq/mL x patient body weight (g)/ the injected dose of FDG activity (MBq). The region of interest (ROI) included the area of

maximum uptake value corresponding with the primary tumor with an isocontour of 50%.

Immunohistochemical procedures

Paraffin-embedded tissue blocks of the primary tumors were processed for immunohistochemical (IHC) analysis on tissue microarray. The tissue microarray was constructed for staining after deparaffinization, using the following primary antibodies with a dilution and expression against: 1:750 HK-II (Chemicon international, AB3279), 1:750 GLUT-I (Chemicon international, AB1340), 1:1000 p53 (Dako, M7001),1:50 VEGF-C (Santa Cruz Biotechnologies, sc9047), 1:50 HIF-Iα (Neomarkers, MS-1164) and 1:300 MIB-I (Dako, M7240).

Table 1. Patients and tumor related characteristics and correlation between clinical, pathological and biochemical characteristics versus FDG uptake in the primary tumor measured in highest average SUV_{max}

Characteristics	*N (%)*	*r*	*Significance*
Gender		0.10	0.51
Male	38 (81)		
Female	9 (19)		
Age (years)		0.18	0.24
Mean (range)	64 (43-80)		
Histology		0.22	0.13
AC	38 (81)		
SC	9 (19)		
Localization		0.7	0.63
High	7 (15)		
Low	40 (85)		
Tumor length (cm)		0.12	0.42
Mean (range)	5.5 (1-18)		
pT stage		0.23	0.11
T1	5 (11)		
T2	11 (23)		
T3	29 (62)		

T4	2 (4)		
pN stage		0.39	0.01**
N0 (neg)	14 (30)		
N+ (pos)	33 (70)		
GLUT-I		0.07	0.65
Weak	18 (38)		
Moderate	18 (38)		
Intense	11 (24)		
HK-II		-0.44	0.00**
Weak	5 (11)		
Moderate	26 (55)		
Intense	16 (34)		
MIB-I		0.15	0.33
0-10%	4 (9)		
≤ 50%	11 (23)		
> 50%	32 (68)		
P53		0.21	0.16
< 50%	16 (36)		
≥ 50%	30 (64)		
HIF-Iα		0.08	0.61
Negative	33 (70)		
Positive	14 (30)		

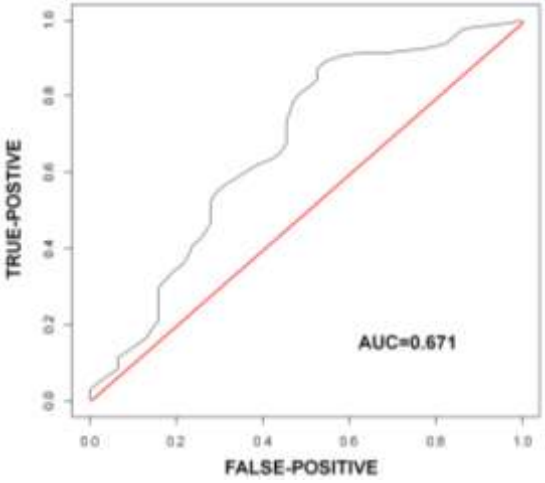
AC: adenocarcinoma, SC: squamous cell carcinoma, Tumor length: lenth of the primary tumor measured on EUS, Stage: pathological stage. The Spearman's Rank test was used for ordinal and nominal variables and the Pearson correlation test for scale variables. *: Correlation is significant at the 0.05 level, **: Correlation is significant at the 0.01 level (2-tailed).

HK-II and GLUT-I expression was scored on a three-point intensity scale (1 = weak; 2 = moderate; 3 = intense). GLUT-I and HK-II immunoreactivity were considered positive when moderate or intense staining was observed homogeneously in the cell membrane and cytoplasm, respectively.[19] Nuclear staining for HIF-Iα and cytoplasmic staining for VEGF were scored dichotomous (0 = no staining; 1= staining). P53 expression was scored negative if less than 50% of the tumor cells were immunoreactive and positive if ≥50% of tumor cells

stained for p53. The proliferative rate was expressed as the Ki-67 index, using the monoclonal antibody MIB-I against the antigen Ki-67. Quantification of proliferation was scored as the number of positive stained tumor cells scattered in decades (0%, 1= less than 10% positive cells; 2= between 10-50% positive cells; and 3= more than 50% positive cells). A score of two or three was considered positive.[20]

Staining sections were evaluated blind by three independent, well-experienced research-physicians who were also unaware of SUVs and clinical outcomes. Any disagreement was resolved in a consensus meeting to obtain final scores.

Figure 1. Time-dependent ROC-curve with highest area-under-the-curve (AUC)



The input in this model were: survival rates with a maximum of 6 years, SUV_{max} values as a continues variable to predict time-dependent (survival time in months) with events (recurrence or death).

Statistical analyses and SUV_{max}

Time-dependent receiver operating characteristic (ROC)-analyses were used to determine the discriminative ability of SUV_{max} for postoperative survival at intervals of 1 (area-under-the-curve, AUC=0.548), 2 (AUC=0.585), 3 (AUC=0.663), 6 (AUC=0.671) and 10 years (AUC=0.578), as described previously by Heagerty et al.[21,22] From this model the interval with the highest AUC value was at 6-years and a SUV_{max} cut-off value of 3.67 predicted survival with the

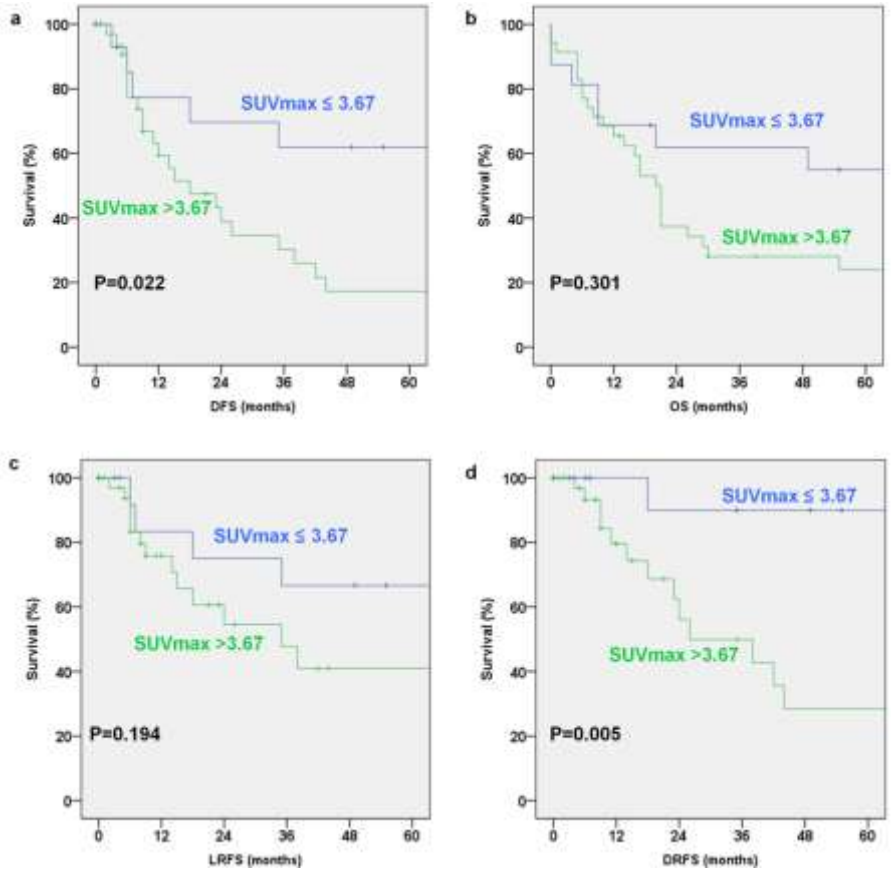
highest degree of a true positive rate (80%) and lowest false negative rate (< 50%) (Figure 1).

We analyzed the association between SUV_{max} (≤ 3.67 vs. > 3.67) with biomarker expression and clinicopathological factors (tumor length <5 vs. ≥5 cm, upper vs. lower localization, tumor invasion T1-T4, and nodal metastases N+ vs. N-). The Pearson test was carried out for scale variables and the Spearman Rank test for ordinal and nominal variables. Survival was calculated according to the Kaplan-Meier method and compared using the log-rank test. A p-value <0.05 was considered significant in all analyses. The statistical analyses were performed with International Business Machines Statistical Package for Social Sciences (IBM SPSS, Armonk, New York, USA) version 20.0, except for the ROC-analyses which were performed with R-project Software, version 2.15.1.

Results

Clinical and immunopathological features are summarized in Table 1. Thirty-eight (38/47; 81%) tumors were adenocarinomas and nine (9/47; 19%) squamous cell carcinomas. The majority were T3 tumors (29/47; 62%). Nodal metastases were found in 33 patients (33/47; 70%) and were significantly associated with pre-operative high FDG uptake in the primary tumor (Spearman Correlation 0.39, p= 0.01, Table 1). Tumor length ranged from 1.0 cm to 18 cm with a mean of 5.5 cm.

Figure 2. Kaplan-Meier curves of patients with $SUV_{max} \leq 3.67$ and $SUV_{max} > 3.67$ tumors



Comparison of disease free survival (DFS, 2a), overall survival (OS, 2b), locoregional recurrence free survival (LRFS, 2c) and distant recurrence free survival (DRFS, 2d) between patients with $SUV_{max} \leq 3.67$ and $SUV_{max} > 3.67$ tumors

Survival in relation to pre-operative SUV_{max}

Tumors with a preoperative SUV_{max} of > 3.67 resulted in a worse disease-free survival (DFS) (p=0.022). The 5-year estimated DFS was 17% in the SUV_{max} > 3.67 group and 62% in the $SUV_{max} \leq 3.67$ group (Figure 2a). There was no difference in overall survival (OS) (p=0.301) between these two groups nor in locoregional recurrence free survival (LRFS) (p=0.181, Figure 2b and 2c). Importantly, the $SUV_{max} \leq 3.67$ group had a strong improvement in distant recurrence free survival (DRFS) compared with the SUV_{max} > 3.67 group (p=0.005), resulting in 5-year estimated DRFS rates of 90% vs. 29% respectively (Figure 2d).

The survival in nodal positive patients was determined because of the strong correlation between high SUV_{max} and positive lymph node metastasis (Table 1). Patients with pathological (p) N+ had a worsen DFS and OS as compared with pN0 patients (Figure 3a and 3b). Patients with > 4 lymph node metastases (LNM) also had a strongly reduced DFS and OS compared to ≤ 4 LNM patients (Figure 3c and 3d).

Glucose transporter expression

Positive GLUT-I staining was present in 29 cases (57%), being moderate and intense in 18 and 11 cases, respectively. Eighty-nine percent of the tumors showed either moderate (n=26) or intense (n=16) HK-II staining patterns. The SUV_{max} was considerably reduced in these tumors with high HK-II expression (p= 0.002). Adenocarcinomas had also higher HK-II expression levels than squamous cell carcinomas (p=0.005), though without significant difference in SUV_{max} between both. We found no significant correlation between GLUT-I expression and the SUV_{max} (p= 0.65) nor between HK-II expression and GLUT-I expression (p =0.49).

Proliferation, apoptotic and hypoxic marker expression

The proliferation index was classified by the levels of MIB-I expression. Eleven tumors (11/47, 23%) were moderate immunoreactive and 32 tumors (32/47, 68%) intense. Sixty-four percent (30/47) showed immunostaining against p53 expression in ≥50% of the tumor cells. There was no significant correlation between the MIB-I expression and the SUV_{max} in the primary tumor (p= 0.33), nor between p53 expression patterns and the SUV_{max} (p= 0.16). HIF-Iα was expressed in 14/47 (30%) of the resected esophageal specimen and was not significantly related to the SUV_{max} (p= 0.33).

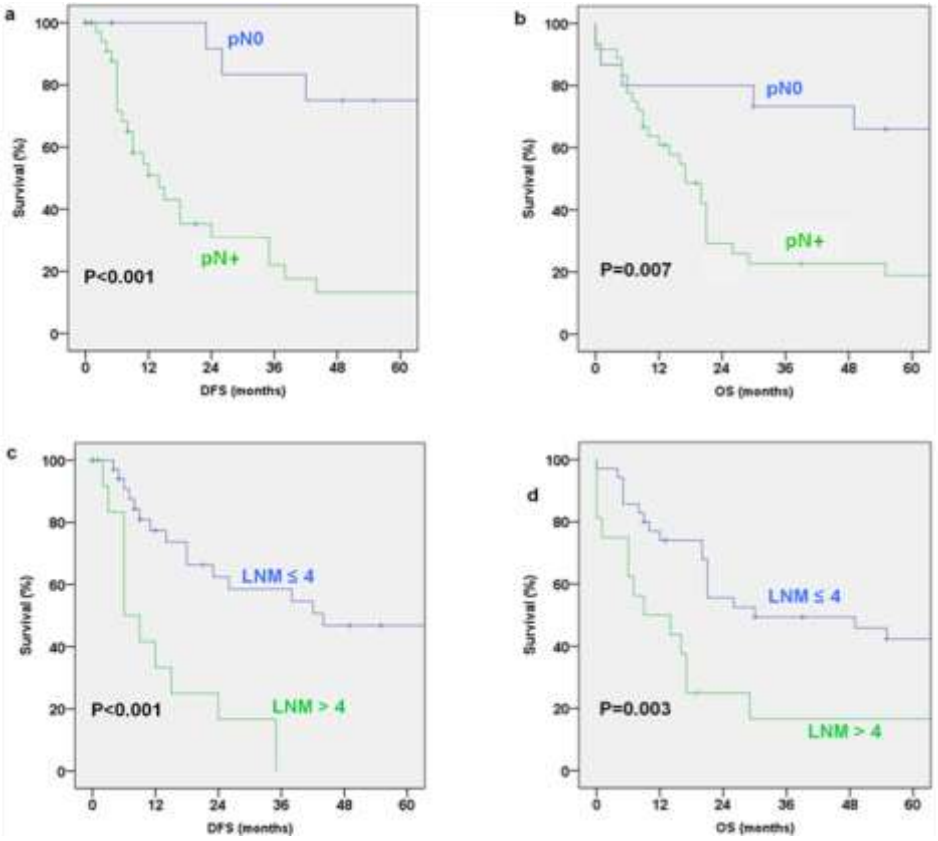
Angiogenesis marker expression

All tumor cells in this study population were intensely immunoreactive to anti-VEGF-C. This intensive VEGF-C staining was also found in connective tissue and stroma cells. As immunoreaction was uniform in all cases, staining against the VEGF-C was not scored and refrained from further expression analyses.

Survival in relation to selected biomarkers

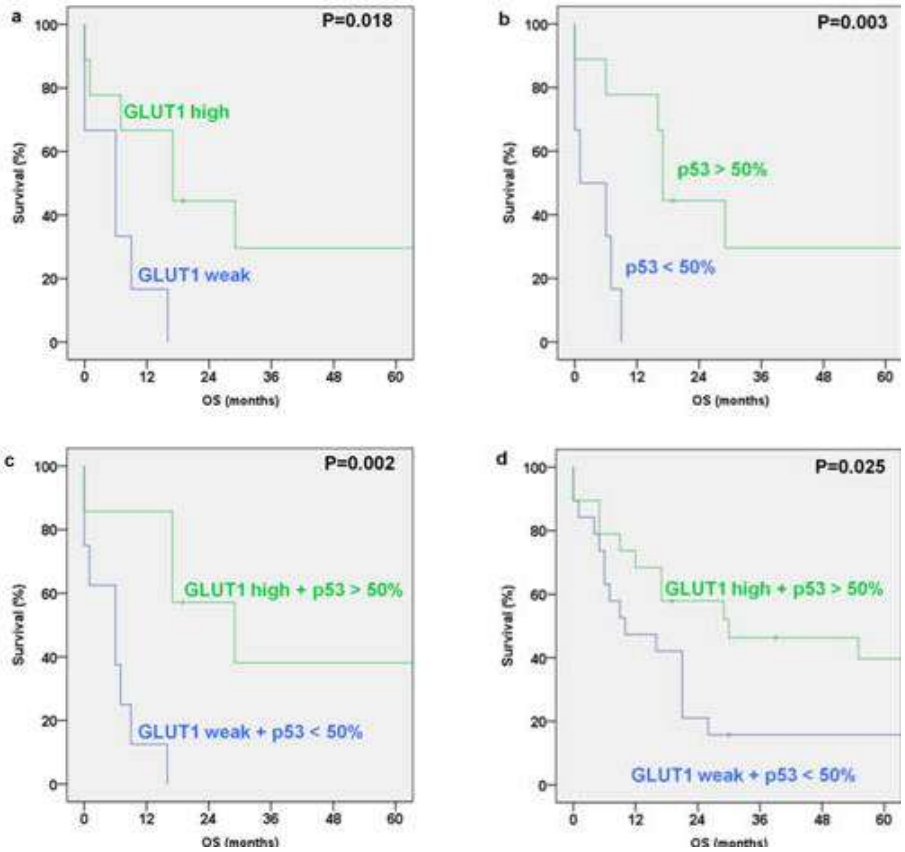
When we selected for only patients with more than four lymph node metastases (>4 LNM, N=15), we found weak GLUT-I expression and loss of p53 tumors to have a significantly worse OS (p=0.018 and p=0.003, Figure 4a and 4b). The 5-year estimated OS was 0% in weak GLUT-I and 30% in high GLUT-I expressing tumors (Figure 4a). Similar, the 5-year estimated OS was 0% in tumors with loss of p53 expression and 30% in p53 expressing tumors (Figure 4b).

Figure 3. Kaplan-Meier curves of patients with tumor positive nodes (pN+) vs. tumor negative nodes (pN0) and patients with lymph node metastases (LNM) ≤ 4 vs. LNM > 4



Comparison of disease free survival (DFS) and overval all survival (OS) between pN+ and pN0 (3a and 3b respectively) and between LNM ≤ 4 and LNM > 4 (3c and 3d respectively)

Figure 4. Overall survival of patients with different GLUT-I and/or p-53 expression and with > 4 lymph node metastases (LNM) or advanced stages of esophageal cancer



Comparison between high and weak GLUT-I expression (4a) and between >50% and <50% p-53 expression (4b) in patients with > 4 LNM. Comparison between the combination of high GLUT-I and p53 expression vs. weak expression in patients with >4 LNM (4c) and in patients with cN+ and/or cT3/cT4 (4d)

The OS in combined p53 and GLUT-I expression was investigated too. In > 4 LNM patients, loss of p53 expression and weak GLUT-I expression negatively impacted the OS (p=0.002, Figure 4c). In patients who should receive a pre-operative FDG-PET according to current guidelines (cN+ or cT3/T4 patients, N=38), the combination of p53 loss and weak GLUT-I expression greatly reduced the OS (p=0.025, Figure 4d). Moreover, the 5-year estimated OS was 16% in tumors with loss of p53 and weak GLUT-I expression and 40% in tumors

with high p53 and high GLUT-I expression (Figure 4d). The expression of the other biomarkers (MIB-1, HK II, HIF-Iα and VEGF) did not correlate with survival.

Discussion

The prognosis in EC remains difficult to assess, despite major advances in diagnostic and treatment strategies. The present study shows that FDG-PET and FDG uptake-related biomarkers, including GLUT-I and p53 provide additional prognostic information in patients with EC who are eligible for surgery.

Several studies have recommended to use the SUV_{max} of FDG as a prognostic factor. Fukunaga et al. described a significant survival difference between low and high FGD uptake esophageal tumors (55% versus 30% two-year DFS, respectively).[23] In a previous study, we also observed that patients with a high SUV uptake had a poorer survival compared to those with low SUVs.[5] However, multivariate analysis in that study showed that SUV uptake was not an independent predictor of survival. This study was performed in patients who were fit enough for surgery and in those without evidence of metastases. In the present study we only analyzed SUV uptake in patients who underwent a curative surgical (R0) resection. Patients with a relatively low FDG uptake ($SUV_{max} \leq 3.67$) pre-operatively had a greatly reduced distant recurrence rate and a better DFS. This study underlines the prognostic value of FDG uptake in EC, even though recently there has been an ongoing debate regarding whether the prognostic information based on SUV_{max} cut-off value is still retained when patients received neoadjuvant chemoradiotherapy.[24,25] With the introduction of neoadjuvant chemoradiation, other parameters like delta-SUV_{max} (SUV_{max} difference pre and post neoadjuvant chemoradiotherapy) or FDG-PET-avid positive local lymph nodes may be more useful.[25,26] Importantly in patients that received definitive chemoradiotherapy prognostic information based on SUV_{max} cut-off value is retained.[27] High preoperative FDG uptake was significantly associated with lymph node metastases. This is in line with previous research in which preoperative FDG uptake was an independent predictor of lymph node metastases in esophageal squamous cell carcinoma.[28,29] This study is to our

knowledge the first to confirm these results in a radical resected predominately esophageal adenocarcinoma cohort.

Glucose transporters play an important role in glycolysis upregulation and levels of GLUT-I expression are thought to be a strong adverse prognostic factor.[8,9] Previous research has shown a significant correlation between FDG uptake and GLUT-I expression.[30] Interestingly, we observed no correlation between FDG uptake and GLUT-I expression. The majority of our patients had an adenocarcinoma, whereas the patients in previous studies predominantly had squamous cell carcinoma. In line with our results, Westerterp et al. recently observed that cytoplastic GLUT-I expression and VEGF expression did not correlate with FDG uptake in patients with adenocarcinoma.[31]

As expected, loss of p53 was strongly associated with a worse survival. Indeed, the combination of p53 loss and weak GLUT-I expression predicted a worse prognosis in patients with cN1 and/or cT3/cT4 tumors. We also demonstrated a survival benefit in selected patients with >4 lymph node metastasis and higher expression rates of GLUT-I. However, this seems in contrast to other previous research where higher GLUT-I expression was related to reduce survival.[32] A possible explanation could be the amount of mucus producing cells of the diffuse type adenocarcinoma that may lead to confounding results, as previously shown by Stahl et al. that mucus producing cells have a reduced FDG-PET uptake.[33] Furthermore the relation between GLUT-I/HK-II expression and actual FDG uptake is debatable.[34] Future research should investigate the combination of p53 and GLUT-I expression in pre-treatment biopsy specimen in stratifying treatments accordingly.

We are aware that the present study has some limitations, including a relatively low number of patients and the fact that patients with cN positivity or cT3/cT4 esophageal cancer did not received neoadjuvant chemoradiation. Although, the data for this study were acquired during a time period that neoadjuvant

chemoradiation was under study and different guidelines were used around the world, it gives us the opportunity to analyze the real correlation of SUV and biologic markers on survival without inevitable selection of current given neoadjuvant treatment. Recently European experts have integrated different European guidelines to one single guideline.[35] Hopefully this will increase the overall quality in the nuclear medicine field of patient care and research. Finally, SUV methodology is affected by many factors, such as patients' size and plasma glucose levels. Although we do believe that we compensated for this by calculating the optimal SUV_{max} cut-of value according to a time-dependent ROC analysis using our own internal dataset. Probably this is an improvement compared to dichotomatization of SUV_{max} based on the median SUV_{max}.

In conclusion, current study shows that pre-operative FDG-uptake strongly predicts lymph node metastases in esophageal cancer patients. Moreover, patients with a SUVmax of > 3.67 had a greatly reduced distant free recurrence rate. In patients with clinical N1 and/or T3/T4 esophageal cancer the additional information of loss of p53 and weak GLUT-I expression showed a strongly reduced overall survival.

Acknowledgments

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Part V

General Discussion and Summary

Discussion and future perspectives

Optimal staging

Esophageal cancer is known for its aggressive behavior. At the time of diagnosis the tumor has often already attained an advanced stage with in more than 50% of cases concomitant distant metastases. Often, patients with esophageal cancer are in poor conditions. At presentation more than half of the patients aren't medical fit enough for curatively intended surgery and/or in a too advanced stage of their disease.[1] For the most advantageous treatment, optimal staging is very important, preventing unnecessary preoperative treatments and surgical explorations. Moreover, it is also necessary for proper evaluation of neoadjuvant chemoradiation therapy and for accurate comparison of treatment results between institutes. FDG-PET, md-CT and EUS/EUS-FNA are advanced diagnostic investigations commonly used in the staging work-up of esophageal cancer today. Comparing the diagnostic qualities, EUS is the most sensitive method to determine tumor invasion and to detect regional lymph node metastases, whereas md-CT and FDG-PET are more specific tests superior in detecting dissimilated disease.[2] When a tumor is situated in the proximal or mid part of the esophagus, a supplementary bronchoscopy is commonly performed. Ultrasonography (US) of the neck or Magnetic Resonance Imaging (MRI) need to be made if the abovementioned diagnostics give cause for it.

In chapter one we discussed the role of external US of the neck in the assessment of cervical lymph node metastases and its impact on decision making about therapeutic strategies. Cervical metastases are described in 15-30% of all thoracic esophageal cancers and up to 50% of patients with a tumor located above or at the level of the tracheal bifurcation. Predominantly supraclavicular node stations and lymph nodes in the recurrent nerve lymphatic chain are involved.[3-7] We described the limited value of routine external US of the neck if following a protocol consisting of EUS and md-CT, and PET in case of

advanced disease. In such staging work-up, external US of the neck does not improve the accuracy of staging nor changes patient management.

Blom et al. also showed no additional value of external US to a negative PET-CT in 170 referred patients of whom 84% was diagnosed with esophageal cancer. They concluded that external EUS can be omitted in the primary workup, although suspect lymph nodes on PET-CT should be confirmed by FNA.[8]

Omloo et al. emphasized the minimal invasiveness and wide availability of external US and concluded one year after our publication that external US of the neck should be part of the routine diagnostic work-up, even after normal CT and PET scanning, since the importance of the potential therapeutic consequences.[9] We agree with the importance and the consequences of missed cervical tumor deposits, however, we would also like to make some comments on the abovementioned study. To start with, they investigated 306 patients with carcinoma's of the esophagus or gastroesophageal junction, in which only 290 patients were staged with an external US of the neck and out of these 290 patients, merely 109 patients underwent a CT scan and an FDG-PET scan. Their conclusions are partly based on the results in 233 patients whom perceived only external US and CT. Thereby, the radiologists who evaluated the test results were not blinded to the results of other, previously performed investigations nor to the clinical information. The interpretation of the US might be influenced by that knowledge. Besides, the participating radiologists were dedicated and highly experienced, implying the excellent accuracy of the external US which may not be applicable to other medical centers. Finally there was not a single, independent test performed as gold standard in every patient.

Indeed, as mentioned in the first chapter, older studies reported specificity rates of external cervical US of 86-95%. However, with the advance of neoadjuvant chemoradiation as option in a tailor-made therapeutic strategy, it is interesting how external US will perform in the post treatment assessment of cervical metastases. Cwik et al. studied the accuracy of external US in 83 patients with

squamous cell cancer of the thoracic esophagus in which 19/83 (22.9%) had cervical lymph node metastases.[10] Twelve of the 83 patients received neoadjuvant chemotherapy; 2/12 (16.7%) showed a complete response on cervical US and 4/12 (33.3%) showed a partial response. 7/83 Patients underwent neoadjuvant chemoradiation therapy in which 1/7 (14.3%) a complete response was achieved and in 2/7 (28.6%) a partial response. They noticed a sensitivity of 100% before and after neoadjuvant treatment, and a 96% pretreatment specificity though they did not mentioned the post treatment specificity. In the future, further investigations are needed to establish more specifically the role of the external US of the neck in nodal assessment before and after neoadjuvant treatments. Though, following the implementation of the PET/CT in the preoperative work-out, the need for an external US of the neck may be phased out finally.

Chapter two and three go into more detail about the value of PET/CT in preoperative staging and decision making. In chapter two we compared software-fusion of md-CT and FDG-PET images with side-by-side FDG-PET/CT reading. Nodal staging improved substantially with software-fusion concerning detection and localization of nodal metastases in 30% of all patients. This resulted in upstaging (2%) and downstaging (5%) but did not lead to changes in resectability. In chapter three we executed a statistic assessment in order to determine theoretically the most favorable staging strategy in esophageal cancer. The PET/CT upfront model was most sensitive (78% vs. 50%) and most specific (94-97% vs. 80%) in detecting not radically resectable esophageal carcinoma's compared to the conventional model (routine CT/EUS and FDG-PET only on indication). In this way 15% of the invasive EUS's could be passed over. Inclusion of FDG-PET to the EUS upfront model enhanced the number of curatively resectable carcinoma's with 13%, while EUS inclusion to the FDG-

PET upfront model just slightly improved (1%) the detection of resectable tumors.

In the conventional staging workup as globally accepted and applied in patients with esophageal carcinoma's, PET/CT is hardly performed as primary routine staging method but only additional on indication. Sensitivity and specificity of EUS, CT, and FDG-PET is respectively 73%-86%; 81%-82% en 81%-91%. The use of an integrated PET/CT increases both sensitivity and specificity for detection of pathological lymph nodes. Lymph metastases without deviant size can be detected more accurate on PET/CT because lymph node involvement is judged on a combination of tumor size, FDG-avidity, and tumor infiltration. It's sensitivity for the detection and localization of suspicious regional nodes is therefore rather high if there is some distance between the node and the primary tumor. To compare, the combination EUS/CT has a sensitivity and specificity of respectively 84% / 67% vs. 70% / 94% in case of PET/CT and 53%-98% / 77%-100% in case of FNA guided biosy.[11-14] Consequently, due to its high reliability, hybrid PET/CT imaging will be very useful in optimizing a proper new treatment protocol. Gillies et al. described a change in the management plan in 17% (34/200) of their study population with occult metastases being detected in 11% with routine PET/CT embedded in the staging strategy compared to md-CT/EUS alone. Gilles et al explain their relatively small increase to the effect of md-CT's being reviewed by a gastrointestinal specialized radiologist with specific expertise in esophageal md-CT at a centralized multidisciplinary meeting before referral for PET/CT.[15]

We saw the same effect in an earlier study in which we examined the value of FDG-PET, called the DIVAPEC study ([13] Diagnostic Value of PET in Esophageal Cancer) and also in chapter two in which we found in 30% staging improvements though without changes in treatment.

In theory, a PET/CT upfront would lead to a more targeted use of fine needle aspiration (FNA) which leads to a better assessment of nodal metastases. We

expect a substantial decrease (20-40%) in the number of randomly used FNA biopsies and redo endoscopies. Consequently, PET/CT guided biopsies may reduce complications such as perforations (0.5-5%), bacterial infections/mediastinitis (0.2-4%) and bleedings (1-4%). Especially obstructing tumors are at risk, in which 25-30% will perforated if the process needs to be dilatated and/or randomly biopted. In near 25% to 33%, an obstructing tumor process cannot be surpassed by EUS making the endoscopist's judgment incomplete and inadequate.[16]

To conclude, the patient burdens will probable decrease by ruling EUS out in a certain number of cases, as is the same for the risks, and the diagnostic work-out can be accelerated. Besides, it will be possible to maintain or even decrease the economic costs. Of course, these hypothetical statements need scientific backing of a prospective trial to verify the cost-effectiveness ratio.

Therefore, a new project has been started in the second half of 2013. In this pilot study we will prospectively compare the PET-CT upfront with a matched control group of patients from the DIVAPEC study.[13] EUS-FNA will also be performed according to the conventional pathway which allows us to count the number of unnecessary EUS investigations and to do a cost analysis.

Regarding future prospects, PET/CT may also be more accurate in the assessment of treatment response after neoadjuvant chemoradiation therapy (CRT). The amount of residual tumor remaining after CRT is an important predictor of outcome and is fundamental for the proper patient selection for surgery.[17,18] All conventional staging modalities have their own limitations. In EUS, up to 6% an EUS cannot be performed because of luminal stenosis with the risk of overstaging residual disease and EUS-FNA is limited by necrosis and fibrosis that frequently occur after CRT. On CT imaging, it is impossible to distinguish accurately between viable tumor and treatment-induced inflammatory tissue and fibrosis. Consequently, PET/CT will gain influence in

initial staging because adequate comparison with a pretreatment PET/CT will be increasingly important for proper therapeutic response assessment of CRT.

A growing number of studies demonstrate that PET/CT may be more accurate than EUS-FNA and CT in the evaluation of therapeutic response to neoadjuvant CRT and the detection of residual viable tumor deposits.[19-21] In a study of Swisher et al, 103 patients with locoregionally advanced esophageal carcinoma's were treated with CRT and surgical resection. At the time of surgery, 56% had a pathologic response to CRT remaining less than 10% viable cells. Post-CRT measurements that correlated with pathologic response were: CT esophageal wall thickness (13.3 vs. 15.3 mm, $p = 0.04$), EUS mass size (0.7 vs. 1.7 cm, $p = 0.01$) and FDG-PET SUV (3.1 vs. 5.8, $p = 0.01$). The highest accuracy for pathologic response (76%) was achieved by post-CRT FDG-PET with a SUV ≥ 4, which was an independent predictor of long-term survival (HR, 3.5, $p = 0.04$). [21] However, a radical esophagectomy is still indicated in those who show good tumor responses without signs of progressive disease, even if the post-CRT imaging modalities are normal, because PET cannot rule out residual microscopic disease.

Future perspectives on imaging

There are several different imaging techniques which do not (yet) participate in current staging strategies, like MRI and sentinel lymph node (SLN) navigation using CT-lymphography (CTLG). These techniques may improve pre- and intraoperative imaging in the future.

MRI imaging has made a number of major improvements in depict esophageal cancer in the last two decades. The very first studies mentioned disappointing results for T1-weighted (T1W) sagittal images of a 1.5-T MRI system regarding T1-2 tumor stages. For correctly assessed T-stages, accuracy of conventional T1W plus T2W 1.5-T MRI scans was found to be 60%.[22,23] Differentiating between <T3 and ≥T3 tumors was insufficient with a sensitivity and specificity of 40% and 63%, respectively. Recently, several studies have evaluated the potential role of MRI imaging in the staging strategy of esophageal cancer, using 1.5-2T MRI's with background body signal suppression (DWIBS) and fast short tau inversion recovery (STIR) fat suppression. Also diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE-)MRI are functional MRI techniques may provide interesting information. Although the data are rather limited, they describe for T- and N-staging similar or even better results for an MRI implemented strategy compared to conventional imaging strategies. In the latest review article, Van Rossum et al. compared all current studies about MRI to calculate sensitivity, specificity, predictive values, and accuracy of MRI for group related outcome measurements in esophageal carcinoma's.[24] They describe high accuracies (81 %) with high-resolution MRI for T-staging and similar assessment of resectability compared with CT. Their systematic literature search revealed sensitivities, specificities and accuracies of conventional MRI for N-staging of 25–62 %, 67–88 % and 56–77 %, respectively.
In the near future MRI has the potential to bring improvement in staging, complementing the limitations of currently used imaging strategies. Moreover,

it's participation in tumor delineation and real-time guidance for RT needs to examined, as is it's role in the assessment of treatment response. In view of the fast developments in the imaging quality of MRI, however, in future studies MRI may prove to become beneficial for early response monitoring to neoadjuvant CRT and restaging after CRT completion. Recent pilot studies showed that functional MRI might be complementally to the limitations of other imaging devices in predicting pathological treatment response and patient prognosis.[25-28]

The sentinel lymph node (SLN) concept has revolutionized the surgical staging of both melanoma and breast cancer over the past two decades. Preoperative and intraoperative identification of the SLN using CT lymphography may also have great advantages for minimally invasive surgery in esophageal cancer patients. SLN navigation could supply more information about lymphatic routes and metastatic nodes and therefore might enable surgeons to perform less invasive surgery with a reduction in the number of lymphadenectomies performed. There are many methods for SLN navigation. Most methods are performed mainly for the identification of SLN intraoperatively, using a combination of three techniques with radioisotopes (isop99mTc-phytate), patent blue V dye, and preoperative CT-lymphography. Preoperative CTLG in combination with intraoperative fluorescent navigation with indocyanine green and an infrared endoscopic camera system may complete the precise detection of SLN and the lymphatic routes from the tumor. However, radio-scintigraphy cannot supply preoperative detailed anatomical information, especially SLN neighboring the tumor cannot detect because of the shinethrough phenomenon. Therefore, tumor-occupied lymph nodes could not be detected preoperatively, and they are also likely to be missed during the operation. Recent studies have shown favorable results for identification of SLN in esophageal cancer. [29-32] Uenosono et al. performed SLN navigation surgery for T1, T2 and T3 patients

with esophageal cancer. One day before surgery they injected (99m) Tc-Tin colloid endoscopically into the esophageal wall around the tumor. They concluded SLN mapping can be applied to patients with cT1 and cN0 esophageal cancer.[29]

The combination of SLN navigation with endoscopic treatments, such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) might become a new less invasive strategy for superficial esophageal cancer. However, introduction of SLN navigation to the gastrointestinal tract is still controversial. SLN biopsies have suggested that the lymphatic drainage of the gastrointestinal tract is much more complicated than the lymphatic drainage of other sites. Anatomical skip metastasis are rather frequent because of the presence of aberrant lymphatic drainage routes outside of the basin. Skip metastases to the second or third compartment of regional lymph nodes were found in 50%–60% of esophageal cancer.[33] Consequently, until now, there is not enough evidence which permits individualized selective lymphadenectomy. Technical innovation including the development of new tracers is expected, which may confirm the accuracy and reliability of SLN mapping in esophageal cancer in the future. Then SLN mapping and SLN navigation surgery might reduce the morbidity and retain the patients' quality of life.

FDG-PET/CT in radiotherapy planning

As we discussed in the previous chapters, FDG-PET/CT has an additional value in the staging process of esophageal and cardiac cancer. Chapter four and five expound the role of FDG-PET/CT in tumor delineation and radiotherapy planning in comparison with CT-based planning among patients with esophageal cancer.

In chapter four we assessed the effect of co-registered FDG-PET information on geographic misses and inter-observer variability in CT-based tumor volume planning for radiotherapy. We found major effects on target volume definition in 61% of the subjects with a rate of 11% of the volume of the PET/CT based clinical target volumes (CTVs) situated outside the CT-based target volumes. Observer variation did not improve with equal concordance indexes of 63–76% for different target volumes. In chapter six we constructed 3D-CRT plans covering target volumes based on CT and on coregistered PET/CT images. We found comparable modifications (10%) in target volumes as in chapter five, leading to inadequately CT-based target covering of PET-avid target volumes in 36% of the subjects. These treatment plan modifications resulted in significant changes in dose distributions to heart and lungs.

However, we used software-based fusion of FDG-PET with md-CT images in our studies. More recently, several studies have used integrated PET/CT techniques for their tumor delineation. Although all of them included rather small numbers of patients (N= 10-36 patients), they established major changes to the GTV by imaging with significant impact on target volume delineation and subsequent radiation dose distributions.[34-40]

The question arises as to whether these changes based on FDG-PET/CT information are correct. First of all, defining tumor margins on PET/CT is affected by in- and expiratory movements, which make tumor deposits shaped elliptic instead of round and which may cause changes in tumor localization.

Yet, these differences in tumor localization are easily abolished by using 4D-PET/CT-imaging to synchronize with the respiratory cycle.

Secondly, accurate alignment is hampered by the fact that there is no standardization of interpretation of the FDG-signal. Several methods to define that delineation are described. Semi-quantitative methods used for target volume definition are automatic contouring based on the use of an FDG intensity level with a threshold of 40% of the maximum SUV, or the use of an isocontour of 2.5 standard uptake value (SUV) around the tumor. Also, sometimes FDG-PET images are visually interpreted. The source-to-background ratio (SBR) technique as described by Nestle et al., uses the mean activity of the liver as reference value for physiological soft tissue uptake of FDG under fasting conditions.[41] In a prospective study of Yu et al., different methods of GTV delineations for primary lesions were examined, based on four different SUV thresholds of ^{18}F-FDG PET/CT and one based on CT ($SUV_{background + 20\%}$, $SUV_{background + 40\%}$, 40% of SUV_{max}, and SUV2.5). They used as gold standard the GTV delineation from pathology.[34] The $SUV_{background + 20\%}$ method estimated gross tumor length most accurate, but reached an unsatisfactory index of conformality for the GTV. In our opinion is contouring based on SBR the method which is superior, because it appeared to be the most accurate and best reproducible.

Another way to validate the use of FDG-PET/CT in target volume delineation, is to determine intra- and interobserver variability and the index of conformality, assuming that smaller differences between different moments of measurements represent more accurate outcomes. Gondi et al. found a mean index of conformality (overlap/union) of 0.46 in 16 patients with esophageal cancer (range, 0.13 - 0.80) and in 62.5% of them led the addition of the FDG-PET data to a smaller GTV with a standardized margin definition based on background liver PET activity.[35] Vesprini et al. evaluated inter-observer and intra-observer variability of the GTV and tumor length in ten patients with gastro-esophageal

cancer. Both decreased with integrated PET/CT-based planning, especially concerning tumor length (inter-observer variability: 72.7% vs. 69.1%, p =0.02, intra-observer variability: 76.2 to 78.7%, p = 0.001).[36]

At this moment, there are no long-term results published that show that FDG-PET/CT based definition of treatment volumes does improve locoregional control and survival. Until then, the radiobiological significance of FDG-PET negative lesions remains unclear because excluding FDG-PET false negative lymph nodes may result in under dosing and thereby possibly ineffective treatment, and including false positive nodes in the target volume may lead to increased radiation fields and thereby possibly late radiation toxicity. In practice, the irradiated volume is not reduced when the FDG-PET is negative in a region with suspicious nodes on other investigations. Prospective studies are needed in which locoregional control, local recurrence positions versus dose distribution and possible side-effects/complication risks are examined.

FDG-PET and prognostic biomarkers

It is general accepted that recurrence rate and time interval to recurrence are highly related to tumor stage, type and grade. With the implementation of neoadjuvant chemotherapy however, these factors are no longer absolute predictors as tumor stage and grade change because of the administered neoadjuvant therapy. More than ever, there is an urgent need to develop and evaluate biomarkers for predicting survival, recurrence and/or treatment response. In that way it might be possible to use tumor markers for selection of patients requiring especial attention regarding to adjuvant therapies and highly invasive thoracotomies.

In chapter six of this thesis, we examined several tumor markers on their ability to provide additional prognostic information. Also the prognostic value of pre-operative FDG-uptake in the primary tumors was measured in SUV_{max}. SUV_{max} > 3.67 strongly predicted lymph node metastases and was correlated with worse disease free survival (DFS; 17% vs. 62% 5-year estimated DFS) and distant recurrence free survival (DRFS; 29% vs. 90% 5-year DRFS) although there was no difference in overall survival (OS). The combination of p53 loss and weak GLUT-I expression showed a strongly reduced overall survival in subgroups with more than 4 lymph node metastases or locally advanced disease (cN1 and/or cT3/cT4 tumors). HK-II, MIB-I, VEGF-C, and HIF-Iα failed to show any correlation with better or worse survival rates. Perhaps this could be explained to a certain extent by the small number of patients in our study population and the fact that divers types of esophageal cancer types were included (grossly adenocarcinoma and squamous cell carcinoma).

Like in our study, SUV_{max} has been correlated in previously published studies with advanced stages of esophageal cancer and with poorer survival.[42-44] Further investigation of tumor markers and SUV_{max} is necessary to provide more insight into the mechanisms of esophageal carcinogenesis. SUVmax seems to be

positively correlated with the expression of GLUT-I in the specimen of primary esophageal tumors when they were not subjected to neoadjuvant therapy. In patients who did undergo neoadjuvant therapy, GLUT-I expression was not significantly increased. It is suspected that hypoxic condition plays an important role in the upregulation of GLUT-I, and that 18F-FDG uptake may be related to the hypoxic condition and microvessel density ESCC. These possible associations have to be investigated in the future.

In the last decade, an overwhelming number of additional tumor markers and tumor genes have been analyzed in relationship to possible survival benefits (in particular miR- 198, , cyclin D1, Her-2/Neu, APC, TGF-b, Endoglin, CTGF, Bcl-2, NF-jB, Cox-2, E-cadherin, b-catenin, uPA, MMP-1,3,7,9, TIMP, TH1/TH2 balance, CRP, PTHrP).[45-47] All of them have prognostic impact because each one is involved in the multiple steps of the complex processes which lead eventually to malignant alteration. Recently, in 243 patients with esophageal squamous cell carcinoma (ESCC), EGFR overexpression was an independent prognostic factor for overall survival and disease-free survival.[42] 5-year OS and DFS rates of patients with EGFR expression were 15.0% and 14.4%, respectively with median survival times of 16.0 months and 11.6 months. In contrast, the 5-year OS and DFS rates for patients with no/low EGFR expression were 39.3% and 37.5%, respectively, with 31.7 and 25.7 months of median survival times. Future studies will be needed to investigate how the EGFR signaling pathway contributes to esophageal cancer progression or chemotherapy resistance in ESCC patients. Then gefitinib or erlotinib could be used for targeting of EGFR to treat ESCC patients with high EGFR expression, similarly to the treatment of certain lung and colorectal cancer patients.[48]

However, presumably in the future it will still not be possible to predict on behalf of a single biomarker the biological behavior of every esophageal tumor. Probably, the combination of multiple genetic alterations will reveal a better

predictor of prognosis. Microarrays for gene expression analysis may disclose important prognostic information by different sets of biomarkers for different types of tumors. New tumor markers or genes will be discovered and associated with tumor progression or dissemination. These may have additional prognostic qualities and offer new adjuvant therapeutic options.

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Summary

In 2011, more than 2,500 people were diagnosed with esophageal cancer or cancer in the area between the stomach and esophagus, which is called "cardia". This number has been fourfold compared to 20 years ago and worldwide, the number of people with esophageal cancer is still steadily increasing. There are two types of esophageal cancer: adenocarcinoma and squamous cell carcinoma. In the Netherlands, as in other Western countries, the adenocarcinoma is the most widespread (1,800 people), especially in men. About 600 people were diagnosed with squamous cell carcinoma, equally in existence between men and women. The rapid increase in incidence is mainly due to the rapid increase of adenocarcinomas in men.
After one year slightly less than the half of the patients with esophageal cancer is still in life (41%) and after 5 years, 1 of 8 esophageal cancer patients (13 %) is still alive. After curative surgery the five-year survival is 37 % to 51 %, depending on the application of neoadjuvant chemotherapy / radiation and which surgical technique. However, more than half of the patients are no longer fit enough for curatively intended surgery due to their poor health and/or advanced stage of their disease.

To determine the best treatment for each esophageal cancer patient, it is important to determine the extent to which a cancer has developed by spreading. This is called staging. For this purpose, every patient undergoes an endoscopic ultrasound (EUS), a multidetector computed tomography (md-CT) and a positron emission tomography (PET) with radioactively labeled glucose (fluorodeoxyglucose; FDG. In the beginning of this thesis the diagnostic qualities of md-CT , FDG-PET and EUS were compared (**Introduction**). EUS is the most sensitive method (sensitivity, 75-90 %) to determine tumor invasion and to detect regional lymph node metastases, whereas md-CT and FDG-PET are more specific tests superior in detecting dissimilated disease. When a tumor is situated in the proximal or mid part of the esophagus, a supplementary bronchoscopy and an external ultrasound (US) of the neck is

performed. A good sequence of these diagnostic tests is essential to prevent unnecessary investigations and costs. PET-CT is not yet widely accepted as standard staging modality, although it is increasingly performed in addition to the existing conventional techniques. In our staging model (standard EUS, md-CT and FDG-PET), a routine external US of the neck has no clinical value because it does not improve the accuracy of staging and it has no therapeutic consequences for patients with cervical metastases (**Chapter 1**). However, we like to stress that external cervical ultrasound is still indicated to achieve cytological proof of lymph nodes suspected for metastasis by guided biopsy (fine needle aspiration, FNA).

When there is suspicion on distant metastases or invasion in surrounding vital structures on behalf of one of the abovementioned studies, histological proof must be obtained and then one can refrain further research and extensive surgery. However, there is still disagreement about the best sequence. In a theoretical, statistical analysis as described in this thesis, the diagnostic value of each diagnostic modality was analyzed, as a single test and also if the results of one or two other tests were already known (**Chapter 3**) .

In a staging work-up with a PET/CT upfront, 15% of renewed "invasive" EUS could be prevented. This order is more sensitive (78% vs. 50%) than the conventional staging model consisting of md-CT, EUS and a selective FDG-PET on indication, with a higher specificity of 94-97% vs. 80% for determine irresectability of an esophageal tumor (**Chapter 3**).

CT and FDG-PET are complementary techniques whereas the CT provides all information about the anatomical structures like a map for hotspots of FDG-uptake. In this way the sensitivity of physiological PET images increases (**Chapter 2 and 4**). This thesis describes the results of fused FDG PET and CT images compared to both techniques used separately. PET/CT fusion improved in 30% of the esophageal cancer patients the nodal staging. This led to up-staging in 2% and down-staging in 5%. In 15% of the cases, certainty and

localization of metastases improved, though without direct impact on resectability (**Chapter 2**).

Addition of FDG-PET has also impact on radiotherapy planning. Currently, modern radiotherapy includes target volume definition based on a planning CT-scan. Target volume definition includes delineation of the gross tumor volume (GTV, i.e., the primary tumor and lymph node metastases); the clinical target volume (CTV, i.e., the GTV plus a safety margin in all directions and the elective nodal areas to cover potential microscopic disease); and planning target volume (PTV) which is automatically generated to account for set-up inaccuracies and esophageal, cardiac and respiratory movements during radiation.
Fusion of FDG-PET and md-CT leads to changes of the CTV in 61% of the patients with 11% of the PET/CT volume situated outside the CT-based target volume. In this way, PET/CT has the potential to avoid "geographic misses" (**Chapter 4**). Geographic mismatches can result in inadequate coverage's, resulting in under dosing and thereby possibly ineffective treatment. Further investigation revealed in 38% of patients with esophageal cancer, PET/CT-based target volumes (PTVs) were inadequately covered by CT-based radiation plans (**Chapter 5**). It should be noted that this assumes that PET/CT represents the true extent of the tumor. One way to determine the validity of PET/CT in target volume delineation is to test inter-observer variability, based on the assumption that lower inter-observer variability represents more accurate delineation. However, addition of FDG-PET/CT had no significant effect on intra- and inter-observer variability, measured in a so called " concordance index ", which was 63-76 % for the different target volumes (**Chapter 4**).

Treatment plan modifications by FDG-PET/CT resulted in significant changes in dose distributions to heart and lungs. Corresponding changes in normal

tissue complication probability (NTCP) values ranged from −3% to +2% for radiation pneumonitis and from −0.2% to +1.2% for cardiac mortality (**Chapter 5**).

For this thesis we examined also different factors on their ability to predict the prognosis of esophageal cancer patients after surgery. FDG-uptake is measured in standard uptake values (SUV). A maximum SUV > 3.67 was a very good predictor for disease-free and distant recurrence free survival for esophageal cancer patients after esophageal surgery. However, there was no difference in overall survival (**Chapter 6**).
Moreover various tumor markers were analyzed; some of them are involved in the regulation of glucose uptake (GLUT- HK- I and II), others regulate cell proliferation and cell death (p53 , MIB I, HIV - Iα , VEGF). Tumor markers related to FDG uptake in the tumor such as GLUT- I and p53 were indeed correlated with survival (**Chapter 6**) in patients who were eligible for surgery. This was in particular true in patients with advanced stages of esophageal cancer or with more than 4 lymph node metastases in which the five-year survival rate was 0% in patients with tumors that have weak/no GLUT -I and p53 expression and 30 % for patients with high GLUT -I and p53 expression.

There are several limitations of our studies described in this thesis. Regarding the PET/CT studies, it should be mentioned that we used PET/CT images, which we assembled with software into PET/CT fusion images and we did not use PET/CT images of a hybrid PET/CT scanner in which both scans are performed simultaneously in one machine. Furthermore, we used data from a prospective previous study, in which all diagnostic tests were rescored by dedicated radiologists and nuclear medicine physicians. Consequently almost all false-negative findings were detected in earlier stage and corrected and therefore it was difficult to reveal any additional value of PET/CT. About the study of

biomarkers, it is possible that more relationships could have been if the group had been larger and we would have separated the effects in adenocarcinomas from the squamous cell carcinomas.

As is often the case with doctoral theses, this thesis also raises new questions and many questions are still unanswered. Second generation PET/CT scans have been developed. It seems likely that with this new PET/CT generation the accuracy will increase, due to higher camera sensitivity and higher resolution. Based on the present results, a prospective study has started to evaluate the proposed staging protocol with an upfront PET/CT in a clinical setting compared to a matched group.

Nederlandse samenvatting

In 2011 kregen ruim 2500 mensen slokdarmkanker of kanker in het overgangsgebied tussen de maag en de slokdarm, de “cardia” genaamd. Dit aantal is verviervoudigd tegenover 20 jaar geleden en ook wereldwijd groeit het aantal mensen met slokdarmkanker gestaag. Er zijn twee soorten slokdarmkanker: het adenocarcinoom en het plaveiselcelcarcinoom. In Nederland, net als in andere Westerse landen, komt het adenocarcinoom het vaakst voor (1800 mensen), en vooral bij mannen. Ongeveer 600 mensen kregen plaveiselcelcarcinoom, waaronder evenveel mannen als vrouwen. De snelle stijging in incidentie komt voornamelijk door de snelle stijging van de adenocarciomen bij mannen.
Een jaar na diagnose is iets minder dan de helft van de patiënten met slokdarmkanker nog in leven (41%) en na 5 jaar is nog 1 op de 8 slokdarmkankerpatiënten (13%) in leven. Na in opzet curatieve chirurgie is de vijfjaarsoverleving 37% tot 51%, afhankelijk van de voor de operatie toegepaste neoadjuvante combinatie van chemotherapie/bestraling en chirurgische techniek. Echter vaak zijn de patiënten in zo’n slechte conditie dat meer dan de helft niet meer in aanmerking voor een in opzet curatieve operatieve ingreep, deels door uitbreiding van de ziekte en deels door een te slechte algehele conditie.

Om een juiste keuze te kunnen maken hoe slokdarmpatiënten het beste te behandelen zijn, is het allereerst belangrijk om de ziekte zo goed mogelijk in kaart te brengen, zodat duidelijk wordt in hoeverre de tumor is ingegroeid en of er sprake is van uitzaaiingen. Dit noemt men stadiëren. Hiervoor ondergaat iedere slokdarmkankerpatiënt een endo-echografie (EUS), een CT-scan en een PET-scan. Bij een endo-echografie wordt via de mond een dunne buis opgevoerd, een endoscoop genaamd. Aan het eind zitten een lampje, een camera en een echoapparaatje. Hiermee is het mogelijk om de verschillende lagen van de slokdarm in beeld te krijgen en om te zien hoe uitgebreid de tumor door deze

lagen groeit (diepte-invasie). Ook is het mogelijk om de omgevende lymfklieren beter in beeld te brengen en zo nodig dunnenaald-puncties te verrichten voor celonderzoek. De afkorting md-CT staat voor multidetector computer tomograaf. Met een md-CT-scan worden de organen en/of weefsels de buik en borstholte zeer gedetailleerd afgebeeld. Bij het maken van een CT-scan wordt gelijktijdig gebruikgemaakt van röntgenstraling en een computer. Het apparaat maakt in enkele seconden een grote serie foto's waarop telkens een stukje verder wordt afgebeeld. Deze doorsneden geven een goed beeld van de plaats, grootte en uitbreiding van de tumor en van mogelijke uitzaaiingen in bijvoorbeeld de lever, longen of het skelet. PET is een afkorting voor Positron Emissie Tomografie. De PET-scan maakt gebruik van het feit dat de meeste kankergezwellen een verhoogde stofwisseling vertonen, waarbij ze meer suiker opnemen dan het omringende weefsel. Er wordt radioactief gelabeld suiker (fluordeoxyglucose; FDG) toegediend, dat door de kankercellen wordt opgenomen. Een camera draait langzaam om de patiënt heen en maakt foto’s vanuit verschillende posities welke daarna gereconstrueerd worden tot één 3-D opname.

Voorin in dit proefschrift zijn de diagnostische kwalificaties van md-CT, FDG-PET en EUS met elkaar vergeleken (**Introductie**). EUS blijkt de beste en meest gevoelige methode (hoge sensitiviteit; 75-90%) om de dieptegroei van de tumor te bepalen en voor het opsporen van locoregionale lymfklieruitzaaiingen. Md-CT en FDG-PET hebben juist een groot onderscheidend vermogen (hoge specificiteit) en zijn daardoor superieur in het opsporen van tumoruitzaaiing op afstand. Wanneer een tumor in het hoogste gedeelte of in het middendeel van de slokdarm zich bevindt, dan wordt op indicatie aanvullend ook nog een onderzoek van de luchtwegen (bronchoscopie) en een echografie van de hals te worden gemaakt. Een goede volgorde van de diagnostische onderzoeken is essentieel om onnodige diagnostiek en kosten te voorkomen. PET-CT wordt steeds frequenter, maar nog niet algemeen toegepast als standaard, alhoewel wel steeds vaker

uitgevoerd als aanvulling op de bestaande conventionele technieken. In het stadiëringsmodel waarbij er wel standaard een EUS, md-CT en FDG-PET wordt vervaardigd, heeft het routinematig doen van halsechografieën geen klinische meerwaarde omdat daardoor de accuraatheid van de stadiëring niet verbetert en het geen therapeutische consequenties heeft voor de patiënten bij wie cervicale klieren worden aangetoond (**Hoofdstuk 1**). Hierbij moet wel worden opgemerkt dat er nog steeds een belangrijke rol voor externe echografie van de hals is weggelegd bij het selectief toepassen voor het nemen van een fijn naald biopt (fine needle aspiration; FNA) van verdachte lymfklieren op PET/CT.

Wanneer er bij een van de bovenstaande onderzoeken verdenking rijst op uitgezaaide ziekte of doorgroei in omringende vitale organen en met zekerheid kan worden aangetoond dat de patiënt niet meer genezen kan worden, dan kan worden afgezien van verder onderzoek en uitgebreide chirurgie. Echter er bestaat nog steeds geen overeenstemming over wat daarvoor de juiste volgorde zou moeten zijn. In een theoretisch statistische analyse zoals beschreven in deze thesis is de diagnostische waarde van ieder diagnostisch onderzoek bekeken zowel voor als het onderzoek alleenstaand werd uitgevoerd, als ook voor als er al één of twee andere uitslagen bekend waren (**Hoofdstuk 3**).
Indien de volgorde van stadiëren FDG-PET, md-CT en EUS zou zijn, dan zouden 15% hernieuwde "invasieve" EUS kunnen worden voorkomen. Deze volgorde is sensitiever (78% vs 50%) dan het conventionele stadiëringsmodel, bestaande uit md-CT, EUS en selectieve FDG-PET alleen op indicatie, met een hogere specificiteit van 94-97% vs. 80% in het vaststellen van een niet radicaal te verwijderen slokdarmtumor (**Hoofdstuk 3**).

CT and FDG-PET zijn technieken die elkaar kunnen aanvullen. De CT verschaft de anatomische informatie over de structuren als een landkaart voor alle plaatsen waar FDG verhoogd wordt opgenomen waardoor de sensibiliteit

van de fysiologische PET-beelden toeneemt (**Hoofdstuk 2 en 4**). In dit proefschrift zijn de resultaten beschreven van gefuseerde FDG-PET en CT beelden ten opzichte van als de technieken afzonderlijk worden gebruikt. Bij de initiale stadiëring bleek PET/CT fusie bij 30% van de slokdarmkankerpatiënten een verbetering van de lymfklierstadiëring te weeg te brengen. Dit leidde in 2% tot een toename in stadium en in 5% van de patiënten tot een lager stadium. In 15% nam de zekerheid toe over de aard en exacte locatie van verdachte lymfklieren zonder directe invloed te hebben op de het wel of niet kunnen opereren (resectabiliteit) (**Hoofdstuk 2**).

Ook had toevoeging van FDG-PET invloed op de radiotherapieplanning. Het is gebruikelijk om de bestralingsplanning, voor welke gebieden bestraald moeten worden, te maken aan de hand van een planningsCT-scan. Deze gebieden noemen we doelvolumes. Er bestaan drie verschillende doelvolumes; de tumor en eventuele uitzaaiingen tezamen worden GTV genoemd (gross target volume). Hieromheen wordt een veilige marge genomen om eventuele microscopische ziekte ook mee te nemen. Het volume dat zo ontstaat wordt CTG genoemd (clinical target volume). Het planning target volume (PTV) wordt automatisch gegenereerd door in alle richtingen 10mm te vergroten om zo onnauwkeurigheden en eventuele bewegingsfouten te bedekken. Wanneer de planningsCT wordt samengevoegd met FDG-PET tot één planningsscan veranderde in 61% van de slokdarmpatiënten het CTG waarbij 11% van het volume zoals dat berekend was met PET/CT buiten het doelgebied viel zoals dat berekend was met alleen CT. Op deze manier kan PET/CT voorkomen dat bepaalde gebieden per abuis niet worden bestraald die wel bestraald hadden moeten worden. Deze gebieden worden “geografische missers” genoemd (**Hoofdstuk 4**). Geografische missers kunnen resulteren in inadequate dekking, wat leidt tot onderdosering met daardoor mogelijk inadequate behandeling. Uit verder onderzoek bleek dat bij 38% van de patiënten met slokdarmkanker de

PTV's die op PET/CT waren gebaseerd niet volledig waren gedekt door het bestralingsplan dat op alleen CT was gebaseerd (**Hoofdstuk 5**). Hierbij moet wel worden opgemerkt dat hierbij er vanuit gegaan wordt dat PET/CT volume het ware volume is dat bestraald moet worden. Een mogelijke maat voor het bepalen van het meest waarheidsgetrouwe volume is de mate van verschillen tussen meerdere planners onderling omdat aannemelijk is dat die variatie afneemt naarmate het volume meer overeenkomst met het werkelijke volume. Er is gekeken of de toevoeging van FDG-PET van invloed was op die verschillen tussen meerdere radiotherapeuten onderling. Deze persoonsafhankelijke variatie bleef echter gelijk en de mate van overeenstemming, de zogenaamde "concordance index", was 63–76% voor de verschillende doelvolumes (**Hoofdstuk 4**).

De veranderingen in behandelplan door FDG-PET/CT resulteerde in belangrijke veranderingen in de dosis voor het meebestraalde hart en de longen. Er is een maat die aangeeft in hoeverre er kans is dat deze gezonde organen hierdoor schade oplopen, de zogenaamde normal tissue complication probability (NTCP). De bijbehorende veranderingen in NTCP waarden varieerden van −3% tot +2% voor bestralingspneumonitis en −0.2% tot +1.2% voor cardiale sterfte (**Hoofdstuk 5)**.

Verder is er voor het tot stand komen van dit proefschrift gekeken naar mogelijke factoren die de prognose van slokdarmkanker na chirurgie kunnen voorspellen. De mate waarin FDG door een tumorgezwel wordt opgenomen wordt uitgedrukt in standard uptake values (SUV). Een maximale SUV > 3.67 bleek een zeer goede voorspeller voor de ziektevrije en de recidief op afstand vrije overleving voor slokdarmkankerpatiënten na slokdarmchirurgie. Er was echter geen verschil in totale overleving (**Hoofdstuk 6**).

Ook is gekeken naar eiwitten op het oppervlak van een tumorcel of aan de binnenkant van een tumorcel die betrokken zijn bij de opname van suiker

(GLUT-I en HK-II), als ook naar eiwitten die celdood en celgroei reguleren (p53, MIB-I, HIV-Iα, VEGF). Deze eiwitten worden ook wel biomarkers genoemd. FDG-PET en biomarkers die gerelateerd zijn aan FDG opname in de tumorcel zoals GLUT-I en p53 zijn inderdaad gecorreleerd aan overleving bij patiënten die in aanmerking kwamen voor chirurgie (**Hoofdstuk 6**). Dit bleek met name in patiënten in een gevorderd stadium of met meer dan 4 lymfklieruitzaaiingen waarbij de vijfjaarsoverleving 0% was bij patiënten met tumoren die weinig tot geen GLUT-I en p53 tot expressie brachten en 30% voor patiënten met hoge GLUT-I en p53 waarden.

Er zijn ook diverse beperkingen van onze studies in dit proefschrift beschreven. Wat betreft de PET/CT studies moet vermeld worden dat er gewerkt is met al bestaande beelden die later zijn samengesteld tot PET/CT beelden (PET/CT fusie) en niet met een daadwerkelijke PET/CT scanner waarin beide onderzoeken tegelijkertijd uitgevoerd worden. Ook hebben we gebruik gemaakt van de gegevens van de al eerder uitgevoerde prospectieve Slokop-studie, waarbij door nauwgezet herscoren van alle diagnostische onderzoeken door toegewijde radiologen en nucleair geneeskundigen haast alle fout negatieve bevindingen al in een eerder stadium opgespoord waren en daardoor dus lastig een meerwaarde van PET/CT aangetoond kon worden. Voor de studie naar biomarkers geldt dat mogelijk meer relaties gevonden hadden kunnen worden indien de groep groter was geweest en we separaat naar de effecten in adenocarcinomen hadden kunnen kijken en in plaveiselcel carcinomen.
Zoals vaak het geval is met proefschriften, genereert ook dit proefschrift weer nieuwe vragen en zijn vele vraagstukken nog onbeantwoord. De techniek ontwikkelt zich verder en ondertussen zijn betere, tweede generatie PET/CT scans op de markt gekomen. Het lijkt aannemelijk dat met deze huidige PET/CT generatie met toegenomen camera sensitiviteit en hogere resolutie, de accuraatheid zal toenemen. Gebaseerd op de huidige resultaten is een

prospectieve studie gestart waarbij het voorgestelde stadiëringsprotocol met de PET/CT vooraan in de work-up in de kliniek wordt toegepast en vergeleken zal gaan worden met een gematchte groep.

Part VI

Appendices

List of publications

List of publications

Schreurs LMA, Janssens ACJW, Groen H, Fockens P, Van Dullemen HM, Sloof GW, Pruim J, Van Lanschot JJB, Steyerberg EW and Plukker JThM. Value of EUS in Determining Curative Resectability in Reference to CT and FDG-PET: The Optimal Sequence in Preoperative Staging of Esophageal Cancer? Ann Surg Oncol. 2011 May 6.

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Dankwoord

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In 1000 kleine stukjes
Lag ik op de grond
In 1000 kleine stukjes
De dag dat jij me vond

1000 kleine stukjes
Onderweg naar jou
Ik weet dat 't geluk is
Omdat ik van je hou

Nu samen op weg naar het volgende avontuur…

Curriculum vitae

Curriculum vitae

Liesbeth (Maria Antonia) Schreurs werd op 31 december 1978 geboren te Born. Na het behalen van haar VWO-diploma aan het Gymnasium van het Bisschoppelijk College te Sittard in 1997, studeerde zij aanvankelijk Biomedische Wetenschappen aan de Rijksuniversiteit van Leiden. In 1999 werd zij ingeloot voor de studie Geneeskunde, eveneens aan de Rijksuniversiteit van Leiden waarna zij beide studies simultaan vervolgde.

In het kader van de studie Biomedische Wetenschappen liep zij in 2001/2002 haar eerste wetenschappelijke stage bij het Centre for Human Drug Research en de afdeling Intensive Care van het Leids Universitair Medisch Centrum (LUMC) te Leiden waar zij klinisch onderzoek deed naar de farmacodynamiek & -kinetiek van Furosemide bij pulmonaal oedeem na cardiale chirurgie. Hierna volgde haar afstudeerstage bij de afdeling Neuropathologie van het LUMC in samenwerking met het Nederlandse Instituut voor Hersenonderzoek te Amsterdam, deze stage was getiteld "Immunohistochemisch onderzoek naar de rol van autoimmuniteit in de pathogenese van narcolepsie". Zodoende behaalde zij haar docteraalexamens in maart 2002 (Geneeskunde) en december 2002 (Biomedische Wetenschappen). De co-schappen werden doorlopen in verschillende klinieken te Leiden, Leiderdorp en Den Haag, welke op 22 oktober 2004 werden afgesloten met het arts-examen.

Aansluitend werkte zij één jaar als arts-assistent bij de afdeling Chirurgie van het Spaarne Ziekenhuis te Hoofddorp. In 2006 startte zij met het promotie-onderzoek waarvan dit proefschift het eindresultaat is. Zij werd in 2007 toegelaten tot de opleiding Chirurgie welke werd gevolgd aan het Universitair Medisch Centrum Groningen (opleider: prof. dr. H.J. ten Duis) en in het Medisch Spectrum Twente (MST) te Enschede (opleider: dr. W.J.B. Mastboom, later dr. J.M. Klaase). Op dit moment rondt zij haar differentiatie in de Traumachirurgie af bij prof. dr. A.B. van Vugt (MST).